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VOLUME IV *January, 1956* NUMBER 1

PELVIC FINDINGS IN WOMEN PAST THE AGE OF 65*

DEANE M. FARLEY, M.D.† AND JOHN R. WOLFF, M.D.‡

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Geriatric gynecology has become an important clinical sub-specialty. The interest of our profession in the problems of the postmenopausal woman is well exemplified by the many previous reports presented to this society and recorded in our journal.

To form a basis for understanding these problems, however, we must know what to expect in the apparently normal healthy geriatric woman. Although it is well said that no woman ever grows old, we do recognize that atrophic changes will develop in the genital structures following the cessation of ovarian function. Do these "senile" changes produce uncomfortable symptoms? Does this atrophy lead to the development of pathologic conditions requiring therapy? Would not controlled prophylactic estrogen therapy prevent such atrophy and its resultant change in anatomic structure and pathologic state?

To help answer these and other questions we have reviewed the findings in 209 women, 65 years of age and over, who came to the Cancer Prevention Center of Chicago for examination during the past two years. The Cancer Prevention Center of Chicago is an educational institution. Only presumably healthy patients are admitted for study. When abnormalities are found they are reported to the patient's family doctor. Well patients are told to see their physician in one year and to have him repeat this yearly health check-up.

Here then we have a group of seemingly healthy geriatric women for survey. Monroe (1) has presented a similar study of a large group of hospitalized women, many of whom were sick. The group reported here were all presumably healthy when they came to the Cancer Prevention Center.

* Presented at the Annual Meeting of the American Geriatrics Society, New York, N. Y., April 21–22, 1955.

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RESULTS

When asked simply for a presenting complaint, 73 (35 per cent) of the 209 presumably healthy women volunteered distress of one sort or another related to the pelvis (Fig. 1). Then, as a detailed history was taken, 158 (76 per cent) of the women admitted a pelvic complaint.

Figure 2 shows that the largest group of presenting complaints seemed to arise from the rectum—constipation, hemorrhoids, pain, bleeding, itching and diarrhea. On detailed questioning, over four times as many complaints referable to the rectum were discovered, representing nearly half of the patients. Among these, 58 complained of constipation and 53 of hemorrhoids.

Relatively few presenting complaints concerned the bladder, yet on detailed questioning a tremendous increase in such symptomatology was reported.

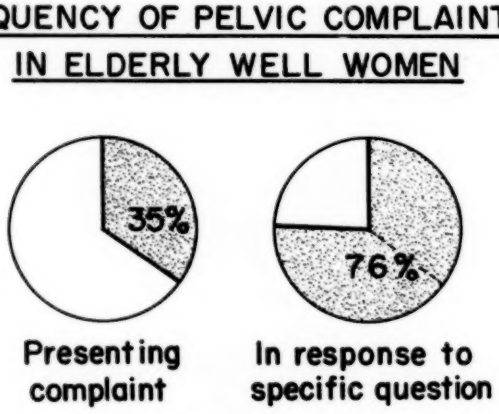
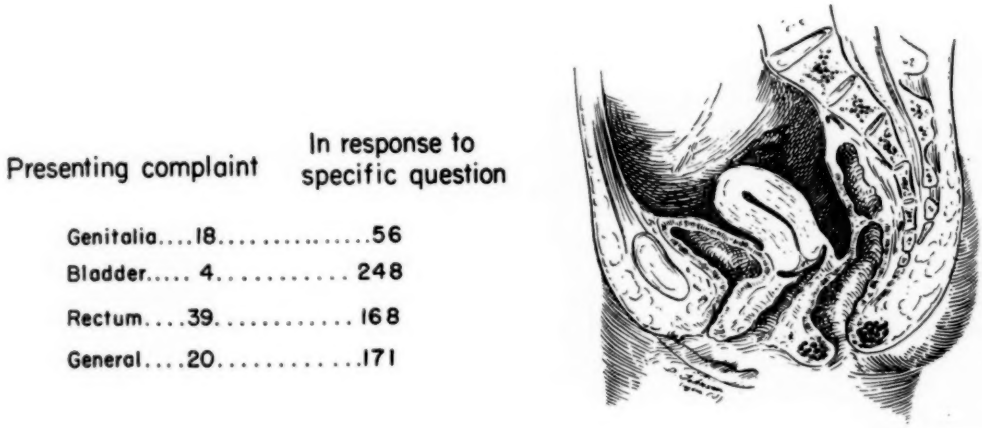


FIGURE 1



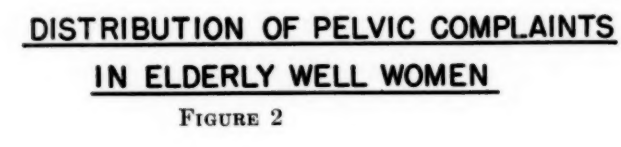


FIGURE 2

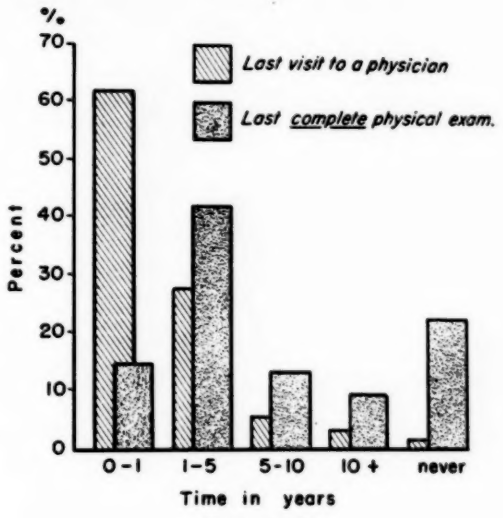


FIGURE 3

Nocturia was noted in 88 patients. Urinary frequency and urgency were very common. Stress incontinence was reported in 30 patients and dysuria was noted 18 times.

The genitalia were the source of a presenting complaint in 18 patients, especially as regards pruritis, leukorrhea and bleeding. In response to detailed questioning 56 patients registered similar complaints; 18 had leukorrhea, 13 had lower abdominal pain, 8 had vaginal bleeding, 6 had pruritis, 5 had an abnormal mass, and 2 had uterine prolapse.

There were other common general complaints, particularly nervousness, fatigue, headaches, irritability, hot flushes and weight loss, which could possibly be related to pelvic disease.

What is the significance of the findings in this group of presumably well geriatric women? The thorough examination given at the Cancer Prevention Center of Chicago was a unique experience for some of these patients. During the course of the history each patient was asked when she had last visited her physician and when she had had her last complete physical examination. Figure 3 shows that most of these women had visited their doctor rather recently. However, almost 25 per cent of them had never had what they considered to be a complete examination. Are physicians reluctant to conduct a thorough examination, including a pelvic one, on an elderly woman? Is it because we fear the examination will be too strenuous, uncomfortable or embarrassing to the patient? Or does she object for the same reason? Is there the false assumption that the pelvic organs are static in the elderly and that other disease is more important?

The fact is (Fig. 4) that 76 per cent of these elderly well patients had pelvic complaints. Furthermore, in 93.3 per cent there were abnormal pelvic findings. Only 6.7 per cent were reported to have a normal pelvis.

Figure 5 illustrates that the commonest finding, senile atrophy, was sufficiently

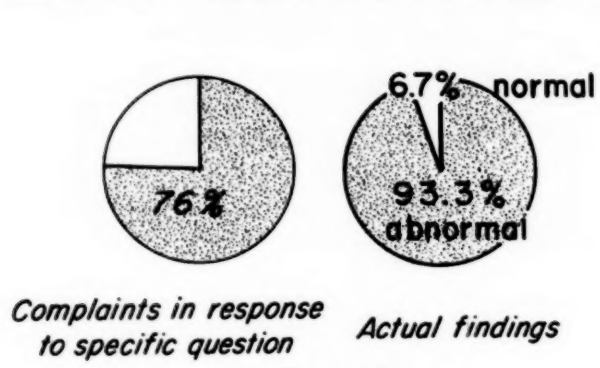


FIGURE 4

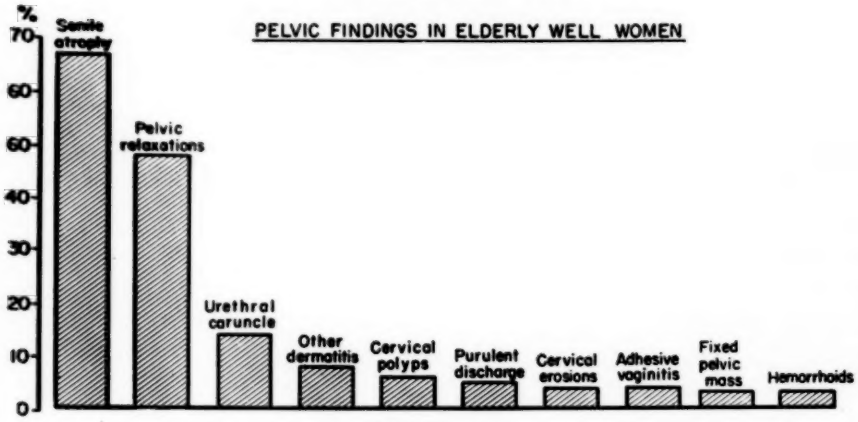


FIGURE 5

evident to be reported as such in 140 (67 per cent) of the patients. It was most apparent in the vaginal mucosa and the cervix, and less common in the labia or in the uterus. The tissues were usually described as simply "atrophic" or "senile," occasionally as "reddened," "shiny," "dry," "telangiectatic," or at times as "inflamed" or "flea-bitten." Atrophy had progressed to the point of adhesive vaginitis in 8 cases—the result of lowered resistance to infection with subsequent adhesive scarring. Other types of vulvar and anal dermatologic disorders were noted in 12 cases, and what appeared to be leukoplakia in 5.

Pelvic relaxations were observed in 100 (48 per cent) of the patients, generally the result of childbirth injuries. Cystocele was noted in slightly over a third of the patients, rectocele in a fourth, and urethrocele in about a sixth. Perineal relaxation was common, but uterine prolapse was seen only four times. Urethral caruncle was present in 29 cases. Other significant findings included cervical polyps in 12 cases, purulent to bloody discharge in 9, cervical erosions in 9, a fixed mass adherent to the uterus in 6, and a fixed mass in the bladder in 1 case. Hemorrhoids were recorded only 5 times, with rectal prolapse in 1 case. There were 5 fibroids, occasional cervical cysts or stenosis, and 1 case of a forgotten pessary.

TABLE 1

CERVICAL SMEARS IN ELDERLY WELL WOMEN

Class I	195 cases
Class II	11 cases
Class III	1 case
Class IV	1 case
Class V	0 case

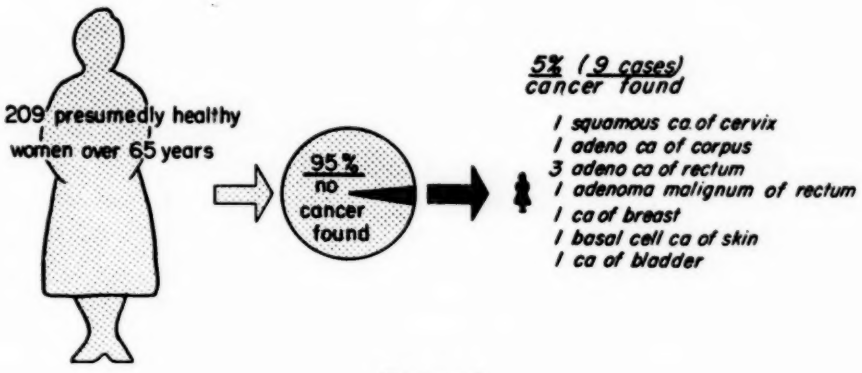

209 presumedly healthy women over 65 years
95% no cancer found
5% (9 cases) cancer found
1 squamous ca of cervix
1 adeno ca of corpus
3 adeno ca of rectum
1 adenoma malignum of rectum
1 ca of breast
1 basal cell ca of skin
1 ca of bladder

FIGURE 6

A cervical smear for cytologic examination, taken in every case and stained by the method of Papanicolaou, was reported Class I in 195 cases, Class II in 11 cases, Class III in 1 case, and Class IV in 1 case (Table 1). A clinical stage III carcinoma of the cervix was the cause of the Class IV smear. The Class III smear was in a case of severe adhesive vaginitis in which no follow-up was available. The Class II smears were from the following cases: 4 of senile vaginitis with a subsequent smear in Class I; 2 of senile atrophy with no reported follow-up; 1 of adhesive vaginitis with a subsequent smear in Class I; 2 of senile atrophy with subsequent smears in Class III, one yielding benign scrapings on curettage and the other a large endometrial polyp; 1 case of senile atrophy with a history of vaginal spotting and the discovery of adenocarcinoma of the endometrium on curettage; and 1 case of adhesive vaginitis following the use of radium five years previously for an unknown condition (not followed).

As a result of our examination and the follow-up information that we have received to date from the patients' private physicians, we know that at least 9 cases of cancer were found, 2 in the genitalia, 4 in the rectum, 1 in the breast, 1 in the skin of the nose, and 1 in the bladder (Fig. 6). This means that of the presumably well women over 65 years of age who came to us for study, at least 1 in 23 had cancer.

DISCUSSION

We were struck immediately by the large number of pelvic complaints which these presumably healthy geriatric women presented. Although many had no complaints at first, detailed questioning uncovered a great many disturbances which not only irritated the patient but frequently worried her as well. With advancing years it seems that a multitude of perhaps minor symptoms combine to cause these patients discomfort and concern. When one notes the fairly large number of general complaints such as nervousness, fatigue, headache, and hot flushes, it is possible that they contribute to the pelvic distress, and there is no doubt that they often do intensify existing symptoms. Whether or not these are significant complaints can be determined only by a thorough examination and evaluation of the findings. This is an important contribution to the peace of mind of these women.

We were frankly surprised to find that 93 per cent of these supposedly well patients had an abnormal pelvis. This completely justified the thorough examination.

The high incidence of atrophic changes, together with adhesive vaginitis and other perineal dermatitis, leads us to re-emphasize the marked difference between the pelvic findings in young women and those in apparently healthy geriatric women. In the latter there is not just a bit of cervicitis, but a deficiency state; the mucous membrane is vulnerable to trauma and infection, and presents a condition which perhaps we should be treating. It is well known that atrophic changes of the skin generally are irreversible, but the skin of the genital area can be easily and effectively rejuvenated many years after the menopause, and all of us have observed the dramatic change in the vaginal mucosa after a brief period of local hormone therapy. Why should we forget the principles of preventive medicine just because the patient is past 65 years of age?

It is surprising that whereas 25 per cent of the women complained of hemorrhoids, they were recorded as present in only 5 cases. If so many complain, possibly we are not recognizing this and other pathologic conditions when they are present.

The various pelvic herniations undoubtedly have some relation to the high incidence of bladder and rectal symptoms. Over half of the patients with stress incontinence showed cystourethrocele. The question arises as to whether surgical correction should not be considered when the patient is active and symptomatic.

Few will deny that these conditions detract from the effort to live serenely and usefully. Does it not follow that our geriatric therapeutics needs invigorating?

SUMMARY

A review of the pelvic findings in 209 apparently well women 65 years of age and over, examined at the Cancer Prevention Center of Chicago, is presented.

Thirty-five per cent volunteered a presenting complaint, and on detailed questioning 76 per cent complained of pelvic distress.

Ninety-three per cent of the patients were reported to have abnormal pelvic

findings; there was senile atrophy in 67 per cent and pelvic herniations in 48 per cent.

Thirteen abnormal cervical smears were found.

These investigations led to the discovery of cancer in 9 patients (4.3 per cent).

CONCLUSION

Presumably well geriatric women have a multitude of pelvic complaints, and they rarely have what may be termed "normal pelvic organs." In fact, urologic and rectal disorders, along with genital atrophy and pelvic relaxations, appear to be more usual that unusual. Cancer can and does occur in this age group. Thorough and frequent examinations are essential to preserving health in elderly people. We need to be more alert to the possibilities of geriatric therapeutics.

REFERENCE

1. MONROE, R. T.: Diseases in Old Age. Cambridge, Mass., Harvard University Press, 1951.

CHRONIC CEREBRAL HYPERTENSIVE DISEASE

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The proportion of old people in our community continues to increase. As a result the long-stay wards of our hospitals have to accommodate an increasing number of elderly patients in progressive stages of mental and physical deterioration. In this clinical miscellany we have been able to identify a group of patients with similar signs and symptoms during life and a uniform post-mortem pattern of lesions to account for these manifestations. This syndrome has been described as "chronic cerebral hypertensive disease" (1). Further study has confirmed our original findings and tends to support our thesis that the lesions and symptoms stem from chronic arterial hypertension.

CLINICAL FEATURES AND POST-MORTEM FINDINGS

The disease is common. In the course of two and a half years we have met with 72 cases among middle-aged and elderly patients. The following case illustrates the clinical features and post-mortem findings.

Case 1

Mrs. S., a widow aged 78, was admitted to Drove Road Hospital, Weston-super-Mare on April 28, 1953. She and her husband owned a small hotel, of which she was manageress. When her husband died ten years previously she gave up the business and went to live with a woman of her own age. Recently she had been unable to do her share of the housework. A year before admission she had her first stroke, which left her with residual palsy of the right upper limb and some dysarthria. She became apathetic, careless in her habits and finally bedfast.

On admission she was able to answer questions rationally. She was obese with a blood pressure of 210/110 mm.Hg. Her face was mask-like with some lid retraction. Her speech was thick and slow. Both knees showed osteo-arthritis clinically and radiologically. This interfered with the walking exercises prescribed.

She was seen at fortnightly intervals during her stay in hospital. A month after admission incontinence of urine developed. When this was referred to in conversation it caused no embarrassment. Reference to her late husband provoked an emotional outburst—weeping.

One year later examination revealed further deterioration. She lay in bed all day staring into space. She could still answer questions but did not normally converse with patients or staff. Her face was immobile and lid retraction more pronounced. She could lie with her head flexed and raised off the pillow for an indefinite period. She was incontinent of faeces and urine and indifferent to her state in this respect. Emotional outbursts were easily provoked.

On July 30, 1954 it was noted she could no longer feed herself. Mastication was slow and awkward with bouts of choking. Her speech had become almost unintelligible. She had signs of congestive cardiac failure. Mental deterioration had progressed.

On October 12, 1954 she had a further major stroke with complete paralysis of the right upper and lower limbs. Blood pressure had fallen to 160/84 mm.Hg. She remained semi-comatose till death on October 17, 1954.

Post-mortem examination revealed:

1. Consolidation of the lower lobe of the right lung,

2. Atheroma of the coronary arteries but no definite obstruction,
3. Laminated aneurysm of the descending aorta.

The brain was fixed in formalin and sectioned later. The naked-eye findings were:

1. The circle of Willis was atheromatous.
2. Coronal section at the level of the mammillary bodies revealed a large slit-like cavity in the left putamen. This cavity extended anteriorly and posteriorly and measured about 5 x 1.2 x 2 cm.
3. Further sections revealed:
   (a) softening and atrophy of the head of the left caudate nucleus,
   (b) multiple small cavities in the right putamen (état vermoulu) and,
   (c) similar cavities in the remnants of the left putamen.

The clinical and pathological findings described in the foregoing case were repeated in subsequent cases. Gradually a pattern has emerged of a chronic disease characterised by sustained arterial hypertension, multiple strokes, emotional lability, pseudo-bulbar palsy, and mental deterioration. Post mortem there are ischaemic lesions particularly concentrated in the distribution of the long perforating branches of the middle and anterior cerebral arteries.

HYPERTENSION

There is no general agreement on what is the lowest acceptable blood pressure reading which will define the hypertensive state. Most of the argument has been concentrated on the 10 mm. in the diastolic reading between 90 and 100 mm. Hg. So far as this group is concerned, 95 per cent of the subjects were unequivocally hypertensives with diastolic readings of over 100 mm. Hg recorded on many occasions. Readings below this level occurred in special circumstances which can be briefly described.

1. The blood pressure may fall after a cerebral thrombosis. We have observed this in some instances and it has been noted by other observers.

2. A fall in blood pressure is the rule after a coronary thrombosis. Coronary disease with clinical manifestations is very common in these cases. One such patient died with a ruptured ventricle following coronary infarction.

3. In terminal cases the blood pressure tends to fall and there may be normal readings for months before death. This is particularly noted in patients with advanced pseudo-bulbar palsy when the dysphagia leads to inanition. Eight of our cases fell into this sub-group.

We are still observing the effects of fluctuations in blood pressure on symptoms and on the course of the disease. So far, it is disappointing to record that the results of lowering the blood pressure are not good. Whether the drop follows the use of hypotensive drugs or occurs in the circumstances just described, the patient shows no improvement. When any clear-cut change has been observed, it has always been for the worse.

The systolic pressures recorded in the group ranged between 140 and 298 mm. Hg. There were 9 cases with readings over 250 mm. on more than one occasion.

EMOTIONAL LABILITY

Emotional lability is the most characteristic symptom of the disease. It may take the form of weeping or laughter and frequently is seen as an indeterminate

explosive phenomenon which neither patient nor doctor can classify. It is often the outstanding symptom and, when this is the case, it is of the highest social importance. The elderly subject who bursts into tears at the slightest provocation soon loses all his friends and even his relatives are glad to be relieved of the burden when he is admitted to hospital.

Typically the emotional reaction is explosive in nature. It starts suddenly and ends suddenly. The secretion of tears lags behind muscular contraction and often we see an emotional storm lasting up to two minutes without the production of a single tear.

In severe cases the patient is mentally inaccessible. Any attempt at conversation provokes a paroxysm of weeping or laughter as the case may be. In 2 of our most severe cases the patients are mentally inaccessible because of pathological laughter. One is a male who tries to answer questions but bursts into silent laughter. Further questions provoke increased spasms and he will end up by striking out at the questioner. The female responds by a wheezy wordless cackle but she never exhibits any signs of rage.

The stimulus for this reaction is always psychological. Pain (for example, taking the blood pressure or giving an injection) does not set it off. Surprisingly, reference to the patient's incontinence or dirty habits, which are almost universal in these cases, does not usually produce an emotional reaction. Its intensity fluctuates and is naturally influenced by environment. A sympathetic nurse will know the trigger subjects which must be avoided in conversation. Generally references to objects of attachment or love in the past—home, occupation one of the family—are the most potent stimuli.

Case 2

Mrs. M. J., aged 64 years, was an ex-music teacher. She was keen on her music and singing and had a good local reputation on the amateur stage.

She was admitted to the hospital after a known three-year history of hypertension with a severe right hemiplegia and aphasia. Her blood pressure was 230/120 mm.Hg. She made a very slow recovery. A year later residual paralysis in the right upper limb was complete and almost complete in the lower limb. Her speech was dysarthric but she could sing after a fashion. She wept at any reference to home or husband, so these topics were avoided in conversation. She attended religious services in the ward and was well-behaved until the congregation began to sing. Half-way through the first hymn she would have an uncontrollable outburst of wailing. She had to be left out of further religious services.

INTELLECTUAL DETERIORATION

Some degree of intellectual deterioration could be observed in all cases. The trend was towards complete dementia in the final stages.

Qualitative changes in personality were among the most interesting clinical findings. These were revealed usually in the history given by relatives, the patient being unconscious of his own defects.

Case 3

Mr. A. G. was at one time a Post Office superintendent in Uganda. He had his first stroke at the age of 73, while driving a car. On November 25, 1952 he was admitted to the General Hospital at Weston-super-Mare in a confused mental state and with paresis of the left side

of the face and left arm. The legs were normal and his blood pressure was 210/130 mm.Hg. He was discharged after two months.

In February 1953 he was admitted to the hospital again, when he was recovering from a further stroke. He was described as having delusions of grandeur and disorientation with regard to time. Again he recovered to some extent and was discharged.

He was admitted under our care to a chronic hospital in January 1954, having had two more strokes. During the two years since his first stroke his wife stated he had become cantankerous and was subject to outbursts of rage, but that he was clean in his habits. At the time of his admission he was cheerful and placid, but disorientated in time and space. He was dysarthric and the left hand was contracted. His blood pressure was 240/130 mm.Hg, and ophthalmoscopy revealed arteriosclerotic changes only. In the course of a month he showed some improvement and could just walk—à petits pas.

In March 1954 he had another "little stroke" followed by general deterioration. His speech became unintelligible and there was some dysphagia. His blood pressure dropped to 180/90 mm.Hg and he became incontinent and dirty in his habits, playing with his faeces and showing complete lack of concern when these habits were remarked upon. By the following May a severe bulbar palsy had developed and the patient was mentally inaccessible. His blood pressure had fallen to 165/90 mm.Hg. He died from lobar pneumonia in August 1954.

The brain, on section, showed a large cavity involving almost the whole of the right putamen at the level of the mammillary bodies. Just in front of this, the cavity involved the internal capsule and caudate nucleus. The left putamen exhibited état vermoulu at this level. In the next section the right putamen contained several minute cavities; there was softening in the internal capsule and the body of the caudate nucleus was almost obliterated. There was a minute cavity in the putamen and in the region of the claustrum on the left side. There was a cavity 3 mm. x 3 mm. in the head of the left caudate nucleus and a number of minute cavities in the extreme heads of both caudate nuclei. There were a few minute cavities to the right of the mid-line in the pons and a cavity 2 x 4 mm. in the white matter adjacent to the right dentate nucleus. The cerebral cortex appeared normal to the naked eye.

Changes in personality varied from one patient to another but there were a few constant findings. In general, the patient was apathetic when his bodily wants were satisfied and was content to sit or lie in the same position for hours at a time. In any attempt at conversation, questions might be answered but there was rarely any attempt to sustain the discourse. Questions often aroused irritation or an emotional storm. Apart from this, the change which impressed us most was in the patient's attitude to his excreta. In the final stage of dementia, as might be expected, the patient was incontinent of urine and faeces. Again in the acute stage of major stroke, incontinence was the rule. The arresting feature in this group of cases, however, was the fact that the incontinence and faulty habits were out of all proportion to the degree of physical and mental deterioration. Thus, an ambulant male who could dress, eat and go out for walks occasionally would leave faeces lying about on the bathroom floor or even in the kitchen sink at his home. Another would humiliate his wife by urinating in his trousers when she took him for a ride in a bus. A patient in the hospital would smile a welcome to the doctor on his ward round while sitting in a pool of urine in her chair. When questioned about the matter she blamed the nurse who never got her to the toilet in time. The patient often retains sufficient insight for the manufacture of most elaborate lies.

Thus a patient whose hands and face are smeared with faeces will say that it is the patient in the next bed who has secreted faeces in his glass or sputum cup. Similarly a male who was persistently smeared all over with faeces every morning complained to the matron that a junior nurse interfered with his sexual organs when washing him.

It might be expected that reference to incontinence or faulty habits would provoke an emotional storm in patients with marked emotional lability but such is not the case. This negative response is in itself impressive. To the detached medical observer who watches the slow and painful acquisition of cleanly habits in childhood it appears that the roots of such behaviour do not go deep. Some of our dirtiest patients still retain a good deal of insight and quite a high degree of intellectual capacity. A teacher who could subtract 75 from 100, add 13 and 14 and still speak a few phrases in French was incontinent and very dirty.

In a few instances the patient's attitude to excretion took an obsessive trend. One male, with rather advanced pseudobulbar palsy continually asked for purgatives and enemata although his bowels moved every day. When in bed he demanded the bed-pan every half hour or so; when he was up out of bed he insisted on being helped to the toilet five or six times a day. Left alone in the toilet he would foul the seat and walls. Similarly, a female graduate with emotional lability would invariably splutter about her "waterworks" on being asked how she was getting on. Laboratory examination ruled out infection and no organic cause could be found for her frequency.

It is difficult to exaggerate the social significance of this particular symptom. Relatives and, occasionally, nurses were convinced the patients could improve their behaviour if they really tried. In the hospital, nurses could often keep a patient clean by "potting" him like children at regular intervals. We have seen improvement in a few cases but it was temporary and relapse occurred with the next "little stroke." In the home, it often threatened the stability of the family and in many cases was the factor which finally determined admission to hospital. To illustrate the depth of feeling which it may provoke we would mention one letter from a son-in-law, when it was suggested that his wife might take her father home for a while. He wrote "Over my dead body that dirty————comes into my house."

Finally we have observed that certain patients, in spite of this symptom, managed to remain popular with the nursing staff or with their relatives. There is in this degradation a vestige of character which survives. Often such a patient is still regarded with affection by his attendants in spite of his lapses in behaviour.

STROKES

A variety of strokes was observed in these patients. Major stroke was common. Sometimes it was followed by extensive residual palsy; sometimes not. The clinical features of major stroke and its neurological consequences are too well known to need description here. In any case, it is not the major stroke but the "little stroke" which is characteristic of the disease. These little strokes are incidents often so slight as to escape recognition by doctor or patient at the time of

their occurrence. They are recognised by their sequelae. The incident may be described as a fainting attack, a "queer turn," a sudden loss of consciousness, or a fall while out walking. After such an incident there is always some alteration in the patient's behaviour. Thus in the hospital a patient who has been sitting up in the ward is reported as having a restless night. We note a deterioration in his behaviour next day, followed by slow improvement until the next incident. These "little strokes" punctuate the course of the disease.

NEUROLOGICAL SIGNS

A characteristic neurological pattern evolves. The gait is quite distinctive. In the "marche à petits pas" the subject takes short steps with the feet wide apart and everted, the knees slightly flexed and the lower limbs rigid. The attitude is one of flexion and the facial features are immobile. In bed a patient will lie with his head raised a few inches off the pillow. He can maintain his head on a "psychic pillow" for minutes if not hours without obvious fatigue. The eyelids are often retracted at rest. When these signs are present, many such patients are labelled as cases of senile or arteriosclerotic parkinsonism. Although there is some resemblance to paralysis agitans, in practice it is easy to distinguish the two diseases. The true parkinsonian tremor is absent, the festinant gait can be distinguished from the "marche à petits pas" and above all the behavioural changes are not seen in paralysis agitans. Finally the blood pressure readings should resolve all doubts in a difficult case.

Extra-pyramidal rigidity was a feature in most cases but there were a few in which it was not demonstrated. The rigidity increased when the patient was irritated. We found it often prevented one from taking the blood pressure in the arm in advanced cases.

Pseudo-bulbar palsy was a distressing feature in many instances.

After major stroke the usual signs of an upper motor neuron lesion are present. Contractures are difficult to prevent in such cases, as the patient is not normally co-operative. It is remarkable how often extensive paralysis after recent stroke clears up completely. When there is residual palsy a positive Babinski reflex persists. In the absence of palsy it is not usually demonstrated.

PSEUDO-BULBAR PALSY

The two cardinal signs in this condition are dysarthria and dysphagia. Dysarthria may be one of the earliest symptoms of the disease. In a typical case the speech becomes awkward, explosive and spluttering. The patient mouths his words, which are uttered singly, each accompanied by a facial contortion. The natural modulation of speech disappears. A sentence will boom into a roar or subside into a whine without reference to its contents. In later stages articulation becomes impossible and all attempts at speech end in grunts or aphonic grimaces.

Mastication and swallowing are affected later than speech as a rule. When dysphagia is established, the clinical picture is characteristic. The movements of mastication are slow and awkward. Food or tablets of medicine placed in the mouth remain there for minutes or even for hours. There is drooling of saliva over

the lower lip. Choking accidents were frequent in our advanced cases and one proved fatal. Death finally occurs in many instances from inanition. Such patients are probably hungry and this may account for the depraved habits noted in some cases. Left to themselves, they will grasp the food with their fingers and stuff as much as possible into the mouth.

Ataxia following on pyramidal and "extra-pyramidal" lesions, together with the concomitant intellectual deterioration, combine to give a picture of a greedy old patient wolfing his food like an animal. In one of our cases a daughter brought in two cooked sausages for her father. The sausages were still united by a piece of "skin." The patient swallowed one after the other and choked. Fortunately a nurse was able to extract both sausages with his fingers.

OPHTHALMOLOGIC FINDINGS

The usual ophthalmoscopic findings were narrowing and "silver-wiring" of the arteries and dilatation of the veins. Exudates and haemorrhages were occasionally seen but they were obviously not part of the essential pathology of the disease. This helps to differentiate the syndrome from malignant hypertension. As might be expected, there is some overlapping between the two syndromes. One of our most typical patients was a young hypertensive, aged 39 years, with exudative retinal lesions. We also observed a patient aged 81 with similar retinal lesions, emotional lability and personality changes. More expert investigation is needed in this field.

PATHOLOGICAL FINDINGS

In every case examined post mortem, multiple small infarcts were found bilaterally in the caudate nuclei and putamina. The diameter of the infarcts, which were small cavities or areas of softening, varied between 2 and 5 mm. These were the only constant macroscopic lesions. Similar cavities were frequently found in the thalamus on both sides. Cavities were only rarely found in the brain-stem, and the globus pallidus seemed to escape altogether.

As might be expected in this age group, and with a history of hypertension, other lesions were found. Thus, large cavities often involved the internal capsule as well as the caudate nucleus and putamen. Such cavities were not bilateral. Large cavities also were found in the region of the external capsule and claustrum, usually involving the lateral aspect of the putamen. These lesions usually corresponded to major stroke in the clinical story.

The mechanism of infarction in these cases is still a mystery and various theories have been put forward to explain it.

Certain anatomical features may account for the distribution of the lesions. Most of the infarcts occur in the territory supplied by perforating branches of the anterior and middle cerebral arteries. Kristenson (2) demonstrated that the flow of blood in the anterolateral ganglionic branches is against the stream in a retrograde fashion. He also demonstrated an annular constriction at the origin of the ganglionic arterioles. The perforating arteries do not anastomose one with another. Thus the territory supplied by the perforating arteries may

be said to be anatomically vulnerable. The globus pallidus is supplied mainly by the anterior choroidal artery which is larger than the other perforating vessels, and this may account for the fact that the globus pallidus escapes infarction.

Hicks and Warren (3), in a study of 100 cases in which they were unable to demonstrate the presence of obstructive vascular lesions, suggest that vasospasm may be an important factor in their production. Another possible factor is the occurrence of thrombosis, although positive evidence of this is seldom obtained histologically. A sudden fall of blood pressure commonly follows major or minor stroke, and also coronary thrombosis. This, in conjunction with the anatomical features described, may induce a sufficient degree of anoxia in the territory of the ganglionic arteries to cause permanent infarction without occlusion of a vessel.

DISCUSSION

This study was originally begun in a series of old people with obvious signs of mental deterioration. A group crystallised out, in whom there were certain clinical findings in common and a uniform pattern of macroscopic lesions post mortem. Gradually our approach to the study has shifted and arterial hypertension rather than senile dementia has become the point of departure.

Hypertension is a very common finding in old age. In the age group somewhere between 60 and 70 years it is probable that there are more hypertensives than normotensives in the population. We cannot from our present study say in how many of these cases of so-called "benign" hypertension will the syndrome of chronic cerebral hypertensive disease develop. Since the study began we have identified 72 cases which satisfied all our diagnostic criteria. Our impression is that it is a common disease; that there is at least one such patient on the list of the average doctor in Great Britain. The average doctor's list contains about 2,000 names.

Any one of the clinical findings we have noted may be observed in certain other diseases. As is well known, emotional lability may be met with in cases of multiple sclerosis, in which it may be accompanied by pseudo-bulbar palsy. Incontinence and intellectual deterioration are common enough in senile dementia and some forms of psychosis. The syndrome described here is defined by the combination of characteristic symptoms and arterial hypertension during life, with a constant and appropriate pattern of lesions post mortem. It is further defined by its evolution over a period of years, its relentless progress to a fatal termination and its punctuation with multiple "little strokes."

We can assign with confidence the neurological findings to the anatomical lesions in the region of the basal ganglia.

This, however, leaves an interesting residue of psychologic lesions unaccounted for. Histologic studies so far (1) have not revealed any significant degeneration in the cerebral cortex. For the moment, therefore, the question arises—can the macroscopic lesions in the diencephalon and midbrain account for the alterations in behaviour and intellectual deterioration we have noted?

Penfield (4) has postulated that the highest integration of behaviour and abstract thought takes place, not in the cortex but in a reticular system which extends from the medulla to the level of the anterior nuclei of the thalamus. This system has connection with all the basal ganglia and with the cortex. The anatomical basis of the system had already been identified by Magoun (5). The lesions we found in our cases were concentrated in just such situations as would interrupt the continuity of this system. The early and specific loss of social accomplishments and abstract thinking in our patients would tend to support Penfield's (4) idea of a "centrencephalic system" in this region.

Further speculation on this very interesting problem must be left to the neurologists. Suffice it to note that we need no longer attribute the peevishness, meanness and faulty habits of these elderly patients to moral turpitude. There are organic lesions to account for them.

Since we have found this syndrome to be relatively common, it may be asked why it has not been recognised and described before now. The fact is that each of the symptoms and lesions has been described in connection with either hypertension or old age, but the synthesis was incomplete. Alvarez (6) first brought the patients in this group to life in his account of little strokes published in 1946.

Emotional lability with pseudo-bulbar palsy has been described by Dejerine (7), without reference to blood pressure. We have no difficulty in identifying the syndrome in published accounts of malignant hypertension whenever there is a series of cases with adequate case histories [Rosenberg (8); Davison and Brill (9)]. The text-book descriptions of cerebral arteriosclerosis contain most of what we have described. Cerebral arteriosclerosis, however, is an unfortunate term. It has pretensions to accuracy which are not upheld in its current usage. In fact it covers many unrelated forms of paralysis, dementia and psychosis in old age.

We have the impression that the incidence of this disease is excessively high among the well-to-do and educated persons of the community. Our series included 4 university graduates and 6 business executives who were at one time in a good way of living. The general run of patients admitted to our chronic hospital derives from the artisan and unskilled working classes. It has to be remembered, that these patients are almost impossible to nurse at home and this may partly account for the social distribution of our cases. Alvarez (6) in 1946 drew attention to the personality changes following minor strokes in well known statesmen. He mentioned the cases of President Wilson and President Roosevelt. Since then Stalin has died of stroke and there have been suggestions that he underwent personality changes during the last six months of his life. It would be interesting to speculate on how far the pathology of the perforating arteries in our elderly statesmen has influenced the course of history. Stroke and emotional lability are familiar enough in high places, but neither singly nor in combination would they justify a diagnosis of chronic hypertensive cerebral disease.

So far, we regret to report that our efforts at treatment have met with no success. Our best hope appears to lie in the Linnean approach at the moment. If we can attain exact definition of the limits of the typical case, clinically and

pathologically, it should soon be possible to recognise the early case among the multitude of hypertensives in this age group. Then perhaps our efforts with hypotensive drugs will yield more encouraging results than we have experienced to date.

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EFFECTS OF HYPOTENSIVE AGENTS ON SUBJECTS WITH CEREBRAL VASCULAR INSUFFICIENCY*

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The use of hypotensive drugs (hexamethonium, hydralazine and reserpine) in elderly subjects with hypertension and cerebral vascular insufficiency has been both advocated and discouraged. The principal objection raised is that a reduction of pressure may impair the delivery of essential substrates and thereby aggravate the manifestations of cerebral vascular insufficiency. Studies of cerebral hemodynamics are particularly important in the evaluation of such drugs, primarily because of the extreme sensitivity of the brain to the ischemia attendant upon reduction of pressure. In previous publications (1, 2, 3) we have discussed the effects of these agents individually, but in order to obviate the possibility of varying reactivity in different groups of subjects, it was considered worthwhile to investigate the action of these hypotensive drugs administered in separate courses to the same patients.

METHOD

The 5 subjects of this comparative study included 4 men and 1 woman ranging in age from 55 to 72 years, all permanent residents of an institution for the aged and chronically disabled. The known duration of hypertension varied from one to twelve years; all had previously sustained one or more cerebral vascular accidents and continued to manifest signs of cerebral vascular insufficiency. All subjects showed mental deterioration, presumably due to cerebral arteriosclerosis.

Baseline evaluation included, in addition to routine procedures, one or more electrocardiograms and estimations of cerebral blood flow, vascular resistance and metabolic rate. Blood pressures were recorded twice daily for at least two weeks prior to therapy, using the standard sphygmomanometric technique. These data were averaged to determine the control blood pressure range. All of the baseline determinations were repeated when it was felt that optimum clinical results had been obtained for each of the three hypotensive agents.

The technique of administration of the three drugs and the collection of experimental data were individualized for each hypotensive agent as follows: Hexamethonium was initially administered intravenously, as recommended by Fries (4). Using this titration dosage as a guide, the drug was administered subcutaneously twice daily in increasing doses until the blood pressure one to two hours after administration approximated 150/90 mm.Hg. The patients were kept flat in bed for at least two hours after administration of the drug. Tests

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of cerebral function were again made during this two-hour period after from ten to twenty-seven days of such therapy.

Hexamethonium was discontinued, and after the blood pressure returned to approximately control values, reserpine therapy was instituted. It was given orally in increasing doses (1.5 to 4.0 mg. per day) until a maximum depression of the blood pressure was reached. The dose was further increased in several instances to assure maximum changes in cerebral hemodynamics and metabolism, if such were to occur.

The data obtained during reserpine therapy consistently demonstrated that this drug did not alter cerebral hemodynamics or metabolism, even in relatively large amounts. Therefore, when hydralazine therapy was instituted, reserpine was continued in small doses (0.25 mg./day) in order to control side effects of hydralazine.

Hydralazine (75 mg.) was given orally daily in three doses of 25 mg. each, and increased by increments of 75 mg. per day until maximum depression of the blood pressure was achieved. Experimental data were obtained after about four months of treatment.

Cerebral blood flow and metabolism were determined, using the Scheinberg and Stead (5) modification of the Kety-Schmidt (6) nitrous oxide procedure. Mean arterial pressures were read directly from a damped aneroid manometer attached to a needle inserted in the femoral artery (7). Blood gas analyses were performed according to the manometric technique of Van Slyke and Neill (8).

RESULTS

The hemodynamic and metabolic data obtained in the control periods and during administration of these three drugs are presented in Tables 1, 2 and 3.

TABLE 1. *Effect of hexamethonium on cerebral hemodynamics and metabolism*

Patient	Age (yrs.)	MAP*		CBF		CVR		$CMRO_2$		$CAVO_2$	
		C	E	C	E	C	E	C	E	C	E
W. W.	64	173	84	42.5	41.5	4.1	2.0	3.3	3.6	7.82	8.62
S. C.	59	153	112	32.4	29.2	4.7	3.8	2.3	2.3	6.89	7.78
A. G.	72	163	98	41.2	44.3	4.0	2.2	2.6	3.3	6.72	7.52
M. M.	55	153	93	40.6	45.8	3.8	2.0	2.2	3.2	5.75	7.05
W. B.	61	148	105	20.3	27.8	7.3	3.8	1.2	1.9	6.77	6.80
Mean values											
	62	158	98†	35.4	37.7	4.8	2.8‡	2.3	2.9	6.79	7.55

* In this and other tables, MAP signifies mean arterial blood pressure in mm. of Hg; CBF, cerebral blood flow in cc./100 Gm. of brain/min.; CVR, cerebral vascular resistance in mm. of Hg/cc. blood/100 Gm. of brain/min.; $CMRO_2$, cerebral oxygen consumption in cc./100 Gm. of brain/min.; and $CAVO_2$, cerebral arteriovenous oxygen difference in vol. per cent. C indicates control and E, experimental.

† Significant; $p < .01$.

‡ Significant; $p < .05$.

TABLE 2. *Effect of reserpine on cerebral hemodynamics and metabolism*

Patient	Age (yrs.)	MAP*		CBF		CVR		$CMRO_2$		$CAVO_2$	
		C	E	C	E	C	E	C	E	C	E
W. W.	64	175	136	45.9	36.5	3.9	3.7	3.3	3.3	7.17	8.95
S. C.	59	112	136	29.2	32.3	3.8	4.2	2.3	2.1	7.78	6.54
A. G.	72	136	152	42.5	39.5	3.1	3.9	2.6	1.6	6.05	4.10
M. M.	55	153	145	50.5	48.3	3.0	3.0	2.2	2.7	4.33	5.66
W. B.	61	140	125	27.4	35.4	5.1	3.5	1.2	2.2	4.43	6.31
Mean values											
	62	143	139	39.1	38.4	3.8	3.7	2.3	2.4	5.95	6.31

* *See* Table 1 for explanation of abbreviations.

TABLE 3. *Effect of hydralazine (Apresoline) on cerebral hemodynamics and metabolism*

Patient	Age (yrs.)	MAP*		CBF		CVR		$CMRO_2$		$CAVO_2$	
		C	E	C	E	C	E	C	E	C	E
W. W.	64	175	124	45.9	44.4	3.9	2.8	3.3	3.0	7.17	6.69
S. C.	59	112	88	29.2	36.3	3.8	2.4	2.3	1.4	7.78	3.86
A. G.	72	136	107	42.5	37.2	3.1	2.9	2.6	2.1	6.05	6.99
M. M.	55	153	115	50.5	52.8	3.0	2.2	2.2	2.9	4.33	5.40
W. B.	61	140	84	27.4	43.6	5.1	1.9	1.2	1.9	4.43	4.36
Mean values											
	62	143	104†	39.1	42.9	3.8	2.4‡	2.3	2.3	5.95	5.46

* *See* Table 1 for explanation of abbreviations.
† Significant; $p < .01$.
‡ Significant; $p < .05$.

The data demonstrate that, in the dose administered, both hexamethonium and hydralazine were effective in significantly reducing the mean arterial pressure. Reserpine alone, even in relatively large doses, did not cause a significant reduction in pressure.

The control values for cerebral blood flow and metabolism were lower than previously noted for normal young subjects and the cerebral vascular resistance was significantly elevated (9). Despite the significant reduction in pressure with hexamethonium and hydralazine there was no significant change in the over-all rate of cerebral blood flow or metabolism. The cerebral vascular resistance was, however, significantly reduced with both drugs. Comparison of the data on these subjects with those previously obtained (1, 2) on larger groups of individuals indicates essentially similar results. The one exception was the failure to obtain a significant increase in cerebral blood flow with the combination of reserpine and hydralazine as compared to the previously reported increase with hydralazine alone.

Mental status. It was difficult to evaluate the mental status of these subjects because of day-to-day variations observed even without drug therapy. Four of the 5 subjects had one or more episodes of acute cerebral vascular insufficiency during hexamethonium therapy, even though they were maintained in the supine position for at least two hours after administration of the drug. They became more apathetic, confused, disoriented and/or even manifested a shock-like state with pallor and clammy skin as late as three to four hours after medication. Blood pressures obtained at these times were never below normal range although they were considerably reduced from the pre-therapy hypertensive levels and possibly even below the usual values recorded during therapy. The increased apathy and somnolence frequently noted during reserpine therapy resembled cerebral depression rather than cerebral vascular insufficiency. Episodes of depression, confusion and shock were not observed during hydralazine administration.

Electrocardiograms. The electrocardiograms taken during therapy were not significantly different from those obtained in the control period. The control tracings showed considerable variation, ranging from the record of a previous anteroseptal infarct in Patient S. C. to a normal tracing in Patient M. M. Subject W. W. had a pattern of "acute coronary insufficiency" consistent with a subendocardial ischemia, but had no symptoms of coronary heart disease. Two patients had left ventricular strain and the electrocardiogram on the fifth subject was interpreted as "myocardial abnormality." It is of interest that the patients with definite evidence of coronary artery disease had several episodes of cerebral vascular insufficiency without clinical or electrocardiographic manifestations of increased coronary insufficiency.

DISCUSSION

A reduction of arterial pressure even in subjects with hypertension and overt manifestations of cerebral vascular disease is warranted, since it may delay the progression of the disease and particularly the development of complications (10). The selection of the hypotensive agent and the degree of reduction in blood pressure deserves special consideration in such cases, as an acute reduction in certain instances may result in an inadequate delivery of essential substrates to the brain.

It is of interest that, even in relatively large doses, reserpine failed to effect an appreciable reduction in mean arterial pressure in our subjects, although a moderate reduction in daily auscultatory blood pressure levels was noted. Cerebral hemodynamics and metabolic values were consistently uninfluenced by reserpine therapy in the dosage employed. It was, however, effective in exerting its tranquillizing and sedative effects, but this result could not be considered desirable in our subjects who were operating at suboptimal levels insofar as the functional organization of the central nervous system was concerned. Reserpine has proved to be useful in the management of elderly disturbed patients and as an adjunct to other hypotensive agents.

Despite the use of the subcutaneous route for administration of hexamethon-

ium, precipitous and unpredictable acute reductions of pressure were noted. Four of the 5 subjects in the present study experienced one or more episodes of acute cerebral vascular insufficiency, even though they were maintained in the supine position during the time the drug was presumably exerting its maximum effect. Most of these episodes occurred when the auscultatory blood pressure was within or even above "normal" range. Apparently in these instances the acuteness of the reduction rather than its magnitude prevented adequate compensatory cerebral vasodilatation; thus delivery of essential substrates (oxygen) to the central nervous system could not be achieved even at these normal pressure levels. Subsequent experiences with other hypotensive agents (11, 12) which also depend upon ganglionic blockade for their action have confirmed the hazards of using such drugs in subjects with already compromised cerebral circulation. It should be pointed out that, since it is impossible to determine the extent of cerebral arteriosclerosis in subjects with hypertension in the absence of overt manifestations of cerebral vascular insufficiency, the use of such drugs in these cases to induce acute reduction of pressure may be equally hazardous.

Even though the degree of reduction in mean arterial pressure and cerebral vascular resistance was of the same order of magnitude with hydralazine as with hexamethonium, episodes of acute cerebral vascular insufficiency were not observed with the former drug. This may be attributed to the fact that hydralazine induces a more gradual and sustained reduction in blood pressure, thus permitting more adequate compensatory cerebral vasodilatation. The simultaneous administration of small doses of reserpine eliminated many of the undesirable side effects (headaches, palpitation, tachycardia) associated with hydralazine therapy.

We have treated 53 patients with hypertensive cerebral vascular disease for as long as twenty-eight months with either hydralazine alone or in combination with reserpine. When therapy was discontinued or placebo substituted, further evidence of cerebral vascular insufficiency developed concomitant with a rise in pressure. The frequency of these occurrences would seem more than circumstantial. Only 2 of our subjects experienced complications occasionally noted during long continued hydralazine therapy; one of these complications was a "butterfly" facial lesion and the other, arthralgia.

SUMMARY

A comparative study of the effects of reserpine, hexamethonium, or the combination of reserpine and hydralazine on cerebral hemodynamics and metabolism was made on 5 subjects with hypertensive cerebral vascular disease. Reserpine alone in moderately large doses caused only a slight reduction of blood pressure and no change in cerebral hemodynamics and metabolism. Its sedative effects were considered undesirable in this particular group of subjects. The subcutaneous administration of hexamethonium was associated with a significant reduction of pressure and of cerebral vascular resistance but no change in either cerebral blood flow or metabolism. Frequent episodes of cerebral

vascular insufficiency were noted and seemed to be related to acute reductions in pressure. The combination of hydralazine and reserpine induced a significant reduction of pressure and cerebral vascular resistance but no change in the rate of cerebral blood flow or metabolism. The undesirable side effects of hydralazine were for the most part eliminated by the concomitant use of small doses of reserpine. In our experience the combination of hydralazine and reserpine seems to be the safest and most effective method for the control of hypertension of patients with cerebral vascular disease.

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HEMOGLOBIN LEVELS IN OLD AGE

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It has been well established that throughout most of adult life men and women differ in the concentration of hemoglobin and the proportion of cells in the blood, and in the red cell count. This is apparently a physiologic difference. Whether it persists with advancing age, if so to what extent, and what are the actual levels of hemoglobin in the blood of older people are questions which have become important because of increasing life expectancy. Only recently have sufficient facts been available from which to attempt answers to these questions, but further observations could profitably be used.

SURVEYS OF HEMOGLOBIN VALUES IN ELDERLY PEOPLE

About five years ago Wintrobe (1) summarized our knowledge of the changes in hemoglobin values of adults as follows: in girls essentially a leveling off at puberty, and in boys a sharp increase during adolescence, when the characteristic adult difference develops; thereafter in both sexes little change up to the seventh decade of life. We now know more about the changes in hemoglobin values in later life, but the actual levels which have been reported by various observers differ sufficiently to make an evaluation of them difficult.

The results of some of the most useful surveys on older age groups are shown in Table 1. Information on hematocrit values and red cell counts are included when they have also been observed. Corpuscular volumes and hemoglobin contents have been calculated when the necessary data were available. The most useful and reliable information from the standpoint of numbers of subjects and division into age groups has been reported since 1950.

If we consider first those surveys in which the subjects were not arranged into age groups, we see that in people 50 to 90 years of age the sex difference in hemoglobin level is still apparent, but is smaller than that characteristic of younger adults. The average hemoglobin of women in this broad age group ranged from 92 to 97 per cent of that in men (2–6). In a recent survey in Halifax (7) we found for people 21 to 40 years of age an average hemoglobin value of 15 Gm. per 100 ml. of blood for 106 men, and of 13 Gm. for 83 women, which was 87 per cent of the male value. Wintrobe's (1) estimation of about 13.5 Gm. per 100 ml. for women in the middle years of life was 84 per cent that for men, which he gave as about 16 Gm.

In those surveys for which the subjects were arranged into various age groups, the tendency toward decrease in the hemoglobin value in men after middle age is notable. In two such surveys (8, 9) there appears to be some recovery in the oldest age groups, and in one (10) there is no particular trend, but in this last the number of subjects was probably too small to support conclusions from the data. In those surveys in which there were large numbers of subjects in the various age groups (7, 11, 12) this progressive decrease in men is most apparent. Some

authors (2, 5, 6, 11) have reported a fall in hemoglobin values in both men and women after middle age or in later life, but supporting data were given in only one instance (11), which happens to be one of those surveys with the largest numbers of subjects. Others (7, 8, 12–15) indicate a fall in men, and no change or a rise in women.

Changes or trends in the red cell count and hematocrit values in old people have been included in only a few surveys. When they have been studied without dividing the subjects into age groups (3, 4, 6), both the red cells and the hematocrit values, as well as the hemoglobin, have been higher in men. Bing's (2) figures indicate that decreasing hemoglobin concentration is accompanied by a decreasing red cell count in men but not in women, but he studied relatively few subjects, and the age ranges of his groups were wide. In Miller's (8) subjects, who were all male, the hemoglobin level fell between the ages of 60 and 70 and rose thereafter, and the red cell count did the same, so that the mean corpuscular hemoglobin did not change. Olbrich (10) found higher hematocrit values in men than in women over 50, but figures were not given for various age groups. He obtained a positive correlation between hemoglobin levels and red cell counts. His figures for mean corpuscular volume, mean corpuscular diameter, and color index (proportional to mean corpuscular hemoglobin), indicated no differences in any of them with advancing age. With regard to specific age groups, however, Olbrich was working with numbers probably too small to discern significant changes. The figures from New South Wales, Australia (11), and from Winnipeg, Canada (12) are better in this regard. The Australian survey showed similar decreases in hemoglobin levels in both men and women in old age, and thus was at variance with most other observations. There was, however, in hematocrit values a tendency to decrease in men and increase in women after middle age, and thus a lessening of the difference between them. Hematocrit values were not studied in the oldest age groups, in which the fall in hemoglobin was apparent. Among the subjects up to 60 years of age on whom both hemoglobin and hematocrit values were obtained, the changes did not affect the mean corpuscular hemoglobin concentration, the only cellular characteristic which could be estimated from the figures. The results of the Winnipeg survey showed that in men from 60 to 90 years of age there was a definite progressive fall not only in hemoglobin but also in hematocrit value and red cell count. In women of the same ages there was a fall in only the number of red cells. In both sexes the changes may perhaps be taken to indicate increases in the size and hemoglobin content of the cells.

The results of the surveys in Canada at Halifax (7) and Winnipeg (12), and in New South Wales, Australia (11) are shown graphically in Figure 1. These surveys were chosen because two of them show other data in addition to hemoglobin values, and because they were based upon larger numbers of subjects in the various age groups than were most of the other studies.

If all the data from various sources are considered, it is clear that after middle age in men there is a progressive fall in the hemoglobin level. Most reports also indicate that in women there is no essential change, even after the menopause. Thus the difference in hemoglobin level between the sexes becomes smaller with

TABLE 1

Hemoglobin Levels and Red Cell Values in Adults and Elderly People

Age (yrs.)	No. of subjects		Red cells (millions/cu.mm.)		Hematocrit (vol. %)		Hgb. (Gm./100 ml.)		M.c.* vol. (cu. μ)		M.c. Hgb. (μμg.)		M.c. Hgb. conc. (%)		Authors. Locality. Year. Reference No.
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
–50	19	51	5.5	4.9			[112]†	[105]							Bing. Copenhagen. 1921. (2).
60–	22	21	6.1	5.1			[104]	[96]							
65–80	73	27	4.61	4.46	41.7	40.4	13.1	12.5	90	90	29	28	31	31	Fowler, Stephens & Stump. Iowa City. 1941. (3).
60–94	50		4.75		42.1		14.1		89		30		34		Shapleigh, Mayes & Moore. St. Louis, Mo. 1951. (4).
60–90		50		4.71		40.8		13.7		87		29		34	
66–85	177						14.4								Hobson & Blackburn. Sheffield, Eng. 1953. (5).
61–87		246						13.8							
50–75	—	—					14.5	13.4					[31]	[30]	Morgan & Gillum. San Mateo Co., Calif. 1954. (6).
50–	—	—			47.1	44.6									
60–64	13		4.74				15.3				32				Miller. Staten Island, N. Y. 1939. (8).
65–69	36		4.49				14.6				32				
70–74	39		4.32				13.7				32				
75–79	36		4.44				14.2				32				
80–84	26		4.51				14.4				32				
40–49	1206						14.1								Med. Res. Council. Throughout Gt. Britain. 1943. (13).
50–59	631						14.0								
60–	214	—					13.6	13.2							
58–69		—						13.0							Olbrich. Edinburgh. 1947. (10).
61–69	10		4.94				13.5				27				
64–69		9		4.86											
70–79	23	20	5.13	4.80			14.2	13.4			28	28			
60–88	38	46			45.1	42.0									
80–88	8		5.10				13.6				27				
80–98		19		4.68				12.8				27			
30–39	50	108					14.2	12.5							Pett & Ogilvie. Throughout Canada. 1948. (9).
40–49	65	95					14.3	12.5							
50–59	38	40					13.7	13.0							
60–79	22	24					14.0	12.3							

26–35	51	49			46.3	40.4							[34]	[34]	Walsh, Arnold, Lancaster, Coote, & Cotter. Throughout New South Wales, Australia. 1949–51. (11).
30–39	398	242					15.8	13.8							
36–45	44	50			45.9	41.6							[34]	[33]	
40–49	250	253					15.7	13.9							
46–55	46	35			46.7	42.0							[34]	[33]	
50–59	165	183					15.7	14.0							
56–65	15	14			44.5	42.7							[34]	[33]	
60–69	101	70					15.3	14.0							
70–79	71	40					15.1	13.4							
80–89	13	25					14.5	12.7							
50–59	127	82					14.5	13.2							Jefferson, Hawkins, & Blanchaer. Winnipeg. 1950–51. (12).
	35	31	5.59	4.85	48	42			86	87	[26]	[27]	[30]	[31]	
60–69	108	24					14.3	12.7							
	35	10	5.38	4.96	47	41			87	83	[27]	[26]	[30]	[31]	
70–79	119	74					14.0	13.7							
	36	26	4.92	4.75	43	41			87	86	[28]	[29]	[33]	[33]	
80–89	94	72					13.7	13.6							
	24	25	4.80	4.71	43	41			89	87	[28]	[29]	[32]	[33]	
30–39		35						13.2							Chaloupka, Leverton, & Diedrichsen. Lincoln, Neb. 1951. (15).
40–49		63						13.0							
50–59		64						13.0							
60–69		32						13.4							
70–79		22						13.4							
30–39	—	—					15.2	13.4							Millar. Indians in Northern Manitoba, Canada. 1951. (14).
40–49	—	—					14.6	13.5							
50–59	—	—					14.6	13.9							
60–79	—	—					14.4	13.8							
21–30	83	44					15.1	12.7							Hawkins, Speck, & Leonard. Halifax, Canada. 1953. (7).
31–40	23	39					14.6	13.2							
41–50	23	39					14.7	13.2							
51–60	65	41					14.4	13.1							
61–70	81	55					13.9	12.9							
71–80	71	71					13.4	13.0							
81–90	28	33					12.4	13.0							

* M.c. = mean corpuscular.
† Percentage of an arbitrary standard.

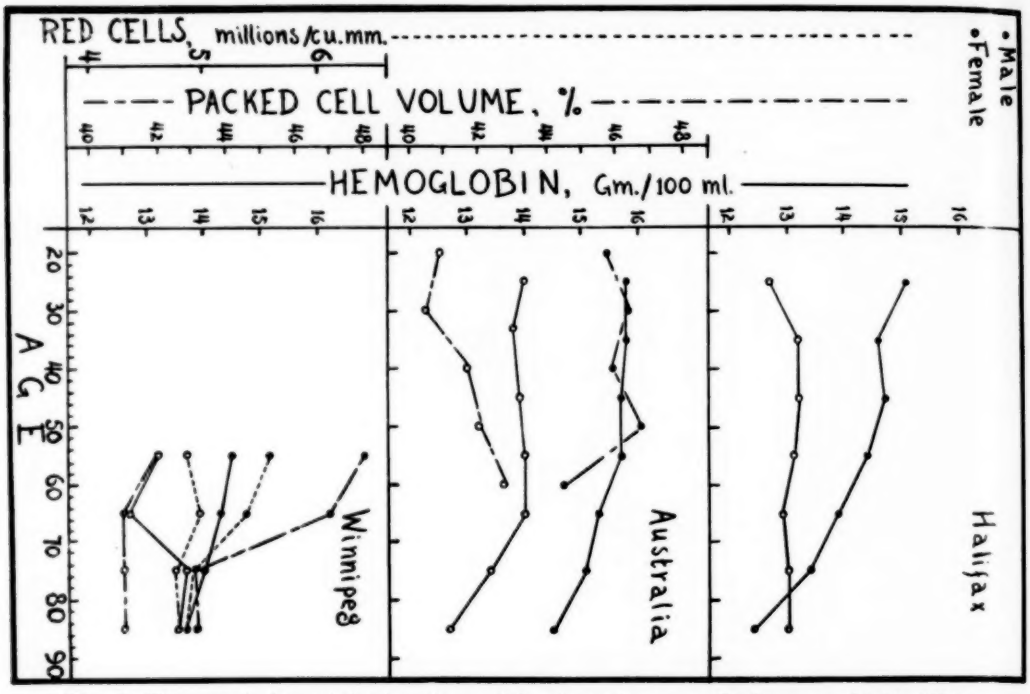

FIG. 1. Changes in hematologic values with advancing age. (References (7, 11, 12)).

advancing age, principally because of the changes in men. There is much less information concerning corresponding changes in the red cell count and hematocrit values, but what there is would indicate that they are not different in direction from those in the hemoglobin level. It would appear that as a result of these changes the red cells do not become microcytic or hypochromic.

The apparent extent of this change does not of course justify a consideration of factors in macrocytic anemia, but there are two things which might be of interest to note in this context. According to Chow (16) old men have lower plasma levels of vitamin B_{12} than young men, and the level cannot be raised to the same extent by oral dosage. Polland (17) found, with histamine tests, that there is a decrease in gastric acid with increasing age in men, but not in women. Values among women were lower at all ages except among the oldest.

THE STORAGE OF IRON

Widdowson and McCance (18, 19) found greater concentrations of iron in various organs, including the liver, of female than of male rats, the difference being greater after maturity. They also found that in sexually mature mice, hens and eels the liver iron was higher in females than in males, but that this sex difference did not exist among guinea pigs, rabbits and perch. Lapicque (20) has reported that the concentration of iron in the liver of women is considerably less than it is in men, and that the difference appears at about the age of 15. There are several reports that the level of plasma iron is lower in women than in men (21–24).

Certain hormones may play some part in the storage of iron. Hamilton *et al.* (25) produced evidence that the adrenal cortex is important in maintaining the plasma iron level of rats. Widdowson and McCance (18) found that if male rats were castrated their liver iron increased to the female level, and that stilbestrol had no effect in castrated males, but caused a slight increase in ovariectomized females. Palmer (26) has reported that the administration of estrone or of stilbestrol decreases the plasma iron concentration in rabbits of both sexes.

A theory that hormonal factors are responsible for a sex difference in the storage of iron is hardly supported by these findings. One of the main difficulties in attempting an explanation is an apparent difference in iron metabolism between the sexes of different species. Furthermore, so far as the evidence goes, man differs from the rat in this regard, and the rat is the animal from which most of the relevant information has been obtained. From the present standpoint it is important to note that the literature provides practically no information on possible changes in the storage of iron in any species at age levels comparable to those of elderly men and women.

ENDOCRINE FACTORS IN HEMATOPOIESIS

Vahlquist (24) noted the characteristic differences in red cells, hemoglobin, and serum iron levels between men and women, and observed that after hysterectomy or prolonged treatment with iron the levels were not significantly raised in women. He pointed out that the sex differences in these blood values were probably governed by endocrine factors. There is considerable evidence from both animal experiments and clinical observations that certain hormones participate in the control of the hematopoietic system. Since sex differences are involved, it is reasonable to expect some influence of the sex hormones, and that has probably prompted much of the investigation on the subject.

Domm, Taber and Davis (27, 28) found that the red cell count of hens and capons was lower than that of roosters, but could be increased to the same level by the administration of testosterone. Conversely the cell count was lowered in capons and normal males by treatment with female sex hormones. The red cell count of ovariectomized hens was affected in the same way by the same treatment. These authors also observed that the gonadotropic activity of pregnant mare serum raised the red cell count of young fowls of both sexes. Similar experiments on rats have given similar results. Steinglass, Gordon and Charipper (29) found that after gonadectomy the red cell and hemoglobin levels decreased in male rats and increased in female rats. If testosterone was then administered to the males the values increased, and if estradiol was administered to the females they decreased. Finkelstein, Gordon and Charipper (30) increased hematopoietic activity in rats by bleeding, sometimes after hypophysectomy or gonadectomy. In all cases the regeneration of red blood cells and hemoglobin was enhanced by the administration of testosterone, and retarded by estradiol. Vollmer *et al.* (31, 32) also used hypophysectomy to induce anemia in rats, which was alleviated by testosterone and intensified by estradiol. McCullagh and Jones (33) have described cases of human hypogonadism, some with pituitary disease, in which

the red cells, hematocrit value, and hemoglobin have been increased, along with the B.M.R., by treatment with testosterone. Such effects of sex hormones appear to be the result of action on the bone marrow (30–32).

Endocrine secretions, not only of the pituitary and gonads but also of the thyroid, appear to act in hematopoiesis. Stern and Altschule (34) observed that after thyroidectomy in human subjects there was a fall in the level of red cells, the hematocrit value, and hemoglobin. Jones (35) found hyperplasia in the marrow of hyperthyroid patients, and hypoplasia in myxedematous patients who were also somewhat anemic. Vollmer *et al.* (36), and Crafts (37) found that the anemia induced in rats by hypophysectomy could be alleviated by the administration of thyroid substance. Crafts (37) induced by thyroidectomy a hypoplasia of the bone marrow similar to that observed following hypophysectomy.

The simplest view of the endocrine relationships indicated by these experiments and observations is that hematopoiesis is supported or stimulated by certain hormones of the thyroid and gonads, which in turn depend upon the anterior pituitary for thyrotropic and gonadotropic activity. This picture is disturbed, however, by de Bias's (38) finding that testosterone increases the red cell count of ovariectomized rats only if the thyroid is present. Gordon and Charipper (39), and Daughaday *et al.* (40) in reviews have pointed out the strong case for a role of the anterior pituitary, the thyroid, and the gonads in hematopoiesis. Gordon and Charipper (39) were of the opinion that the pituitary supplied the initiating hormonal factor. They also thought that the effects were manifestations of effects on general phases of metabolism, in which many tissues were involved. Daughaday *et al.* (40) expressed essentially the same opinion: that the bone marrow was one of many tissues acted upon, and that hematopoiesis was not primarily under hormonal control. All this is of course consistent with sound physiologic thought. Reports of the effectiveness of treatment with iron in the anemia following hypophysectomy (37) and in that of human myxedema (41) indicate the importance of nonhormonal factors.

There is strong evidence that certain sex hormones influence hematopoiesis, and can play an important part in it. Vollmer and Gordon (32) thought that sex differences in red cell count could be attributed to gonadal hormones, and this concept is supported by the findings of other workers. With increasing age in men a decreasing production of androgens could be related to decreasing hematologic values; but in women a similar decrease in estrogen production would not have the same effect.

HEMOGLOBIN AND GENERAL METABOLISM

It is well established that among adults of both sexes the B.M.R. decreases with age. Because of the importance of hemoglobin as a respiratory pigment, some calculations were made in an attempt to find whether any relationship or proportionality exists between the amount of hemoglobin and the expenditure of energy as age advances in both sexes. For this purpose hemoglobin values for people past middle age were taken from the surveys in Halifax (7) and Australia (11), because in these studies large numbers of subjects had been used. The figures from each were treated separately.

TABLE 2

Hemoglobin and Basal Metabolism after Middle Age

Sex and age (yrs.)	Hgb. (Gm./100 ml.)		B.M.R. (Cal.*/M²/hr.)	Basal (Cal./hr.)	Total Hgb. (Gm.)		Ratio, Total Hgb.: Basal Cal./hr.	
	Halifax	Australia			Halifax	Australia	Halifax	Australia
Male								
40–50	14.7	15.7	36.2	67.3	854	912	12.7	13.5
50–60	14.4	15.7	35.4	64.1	822	896	12.8	14.0
60–70	13.9	15.3	34.4	64.1	794	874	12.4	13.6
70–80	13.4	15.1	33.2	59.1	737	830	12.5	14.1
80–90	12.4	14.5	33.0	58.7	682	797	11.6	13.6
Female								
40–50	13.2	13.9	34.5	57.3	571	601	10.0	10.5
50–60	13.1	14.0	33.3	55.3	565	604	10.2	10.9
60–70	12.9	14.0	32.2	55.3	556	604	10.1	10.9
70–80	13.0	13.4	31.3	50.4	538	555	10.7	11.0
80–90	13.0	12.7	30.9	49.7	538	526	10.8	10.6

* Kilocalories.

Fleisch (42) has given figures for B.M.R. which he worked out from those derived from measurement by a number of different workers. These were used in the calculations. Heights and weights for the various age groups of each sex were taken from those obtained in the survey made in Canada in 1953 (43). From these the corresponding average body surface areas were estimated by the DuBois method from the nomogram of Boothby and Sandiford (44). The basal caloric expenditure per hour for a representative individual in each group was then estimated. Gibson and Evans (45) found the average blood volume of adult men and women to be 78 and 66 ml. per Kg. respectively, and Cohn and Shock (46) found no evidence of changes in blood volume between 50 and 90 years of age. These figures, with those for the average hemoglobin concentration of the blood in each age group, and the body weights, were used to calculate the total body hemoglobin representative of an individual of each group. Ratios of the total hemoglobin to the basal energy expenditure per hour were then worked out. The values are given in Table 2.

The use of total rather than basal caloric expenditure would provide better information for the present purpose, but satisfactory average figures for it in the various age groups under consideration are not available. The results of such calculations based on data from various sources must be considered only rough approximations. They do, however, suggest one or two interesting points.

The total hemoglobin in women is less than in men in all the age groups. In both sexes it decreases with age, along with the B.M.R. and the basal caloric expenditure of the body per unit time. In women the amount of hemoglobin associated with basal energy transfer (and we may suppose with total energy transfer) is less than in men. If anything it increases slightly with age, but does not reach the male level. When it is calculated from the hemoglobin levels obtained in the Australian survey, there is no trend in the ratio of hemoglobin to basal calories

in men, but corresponding figures calculated from the survey in Halifax show a slight decrease in this ratio with advancing age. One could only guess as to whether it is sufficient in degree to be physiologically important. That it is probably characteristic of the sex is supported by the findings in other surveys (Table 1), most of which showed trends in hemoglobin values similar to those found in Halifax rather than in New South Wales. If such a trend with age in the relation of total hemoglobin to energy expenditure is real, it could be a factor in the shorter life span of men than of women.

The population of Canada increased from 11.5 millions in 1941 to 14 millions in 1951, and during that time the proportion of males dropped from 51.0 to 50.6 per cent. The highest proportion of males is among the age groups up to early adulthood (47). Up to 65 years of age there are more men than women in most age groups in Canada. Differences become increasingly greater in the other direction after 65. Between 76 and 80 years of age the male population is 99 per cent that of the female; between 81 and 85, 90 per cent; between 86 and 90, 79 per cent; between 91 and 95, 68 per cent; and over 95, 61 per cent (48).

The picture in the United States is similar. The total population increased from about 76 millions in 1900 to about twice that in 1950. In 1900 52 per cent of the population was male; between 1910 and 1930, 51 per cent; in 1940, 50 per cent; and in 1950, 49 per cent. Between 1900 and 1950 the white population 75 years of age and over rose steadily from 1.2 to 2.7 per cent of the total. In 1900 and 1910 men constituted 49 per cent of this fraction; from 1920 to 1940, 47–48 per cent; and in 1950, 45 per cent (49). In the United States, life expectancy at birth increased from 49 to 68 years between 1901 and 1949. The number of people over 65 is increasing by about 400,000 a year, and they constitute about twice the proportion of the population that they did in 1900; but among them women outnumber men 10 to 9. At all ages the life expectancy of American women is greater than that of men. The difference is over five years at birth, and about two years at age 65 (50).

SUMMARY

The results of most surveys which have been based upon adequate numbers of subjects indicate that after middle age the hemoglobin concentration of the blood progressively decreases in men, whereas there is little or no change in women. Thus the sex difference in the hemoglobin level becomes less with advancing years. The smaller amount of data concerning levels of red cells and hematocrit values indicate that any changes in them are probably similar. Existing data would also indicate that these changes with age do not result in microcytic or hypochromic cells.

From what is known of the role of certain androgens and estrogens in hematopoiesis, decreases in gonadal activity which would be expected with advancing age could be important in governing the difference in the trend of hematologic values between men and women after middle age.

If calculations are made of the total body hemoglobin and of energy expenditure, they show that the ratio of hemoglobin to basal energy expenditure is less

in women than in men, but is not characterized by a slight decrease with advancing age as it seems to be in men.

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CHORIONIC GONADOTROPIN IN GERIATRICS

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An important problem in gerontology is the control of obesity and of such commonly associated conditions as diabetes, gout, rheumatism, hypercholesterolemia, arterial hypertension, myocardial insufficiency and certain dermatoses. We know that these conditions are to some extent dependent upon the hormone output of the anterior pituitary lobe and that when they occur in obese patients, their clinical course can be favourably influenced by weight reduction.

Hitherto weight reduction has been difficult to achieve in the aged. Precluded from the sufficiently vigorous forms of exercise available to the young, they have fixed dietary habits which one hesitates to alter drastically unless one can be sure that a dietary deficit will be made up only from abnormal fat deposits and not lead to a depletion of physiologically important reserves of fat, proteins, vitamins and minerals. When an obese patient is given a diet, so restricted calorically as to bring about a loss of weight, it is common experience that the body tends to sacrifice normal fat rather than its pathologic accumulation. This is particularly undesirable in the higher age groups.

The dilemma has been largely overcome by the recent demonstration (1) that small daily doses of chorionic gonadotropin derived from human pregnancy urine selectively render abnormal adipose tissue readily available for making up the deficit of a calorically inadequate diet. This process is accompanied by a rapid breakdown of the adipose tissue, resulting in a marked change in measurements. Only the fat is metabolized, whereas such material as the proteins, blood, vitamins, and minerals which the abnormal tissue contains appear to be fed back into the body. It is apparently for this reason that the gonadotropin-diet method of reducing does not lead to anemia, hypoproteinemia or avitaminosis and renders the supplementary administration of vitamins superfluous, even in cases in which a loss of more than 50 pounds is achieved in a very short time. Moreover, normal deposits, such as the cutaneous fat, not only remain unaffected, but are even restored when previous attempts to reduce weight have depleted them. This has the extraordinary effect of making the face in particular look much younger and fresher than it was before the treatment.

METHOD

A dose of 125 international units of chorionic gonadotropin derived from human pregnancy urine is administered by deep intragluteal injection daily at about the same hour. Larger doses do not enhance the results and a wider spacing is entirely unsatisfactory. During the first three days the patient is told to eat without any restriction. Indeed, if he has previously been dieting, he is asked to eat to capacity, even at the risk of putting on further weight. This is important, firstly to ensure that the normal reserves are well stocked before the reducing diet is started and secondly because it takes about three days before the abnormal fat becomes metabolically available. From the fourth day onward the diet is

restricted to 500 calories daily and made up as follows: two meals only, each containing 100 Gm. of lean meat (veal, beef, chickenbreast, fish, prawns, crayfish) weighed raw and all fat removed before grilling or boiling; a normal serving of low-calorie vegetables or salad, one kind at a time, prepared without oil or butter; one unsweetened rusk, weighing about 10 Gm.; an apple or an orange; salt, pepper and vinegar as desired. There is no restriction on the quantity of fluid ingested but only tea, coffee (without sugar and only 1 tablespoonful of milk in twenty-four hours) and water may be taken. The juice of one lemon per day is allowed for all purposes, but no other drinks of any kind. This food may be distributed at will, provided that no more than the single meal described is eaten at one time. It is essential that this diet be adhered to without the slightest deviation. Under no circumstances can the patient be allowed to substitute caloric equivalents, if the best results are to be obtained.

Without gonadotropin such a diet can be observed by a strong-minded person for about three days, after which there is an intolerable feeling of hunger, weakness and dizziness; but under the peculiar effect of gonadotropin the obese person can continue this diet for several weeks without the least discomfort. There is no hunger; in fact after the first week many patients complain that they can hardly manage the prescribed quantity. Owing to the easy availability of their large potential reserves, they continually have a feeling which they describe as that of just having eaten a large meal.

The treatment should be continued for not less than twenty days (otherwise the weight lost tends to be regained) and not more than forty days, as by that time the so-called gonadotropin immunity develops and renders the injection ineffective. However, after a pause of six weeks, treatment can be resumed if the degree of obesity is such as to make more than one course necessary.

The average loss is about 1 pound per day, though in very fat patients it can be as much as 2 pounds daily. This metabolized fat fully compensates the caloric deficit of the diet. The patient is ambulatory during treatment and, except for the diet, no restriction is imposed upon normal activities. About 70 per cent of the patients have no difficulty in maintaining the weight achieved at the end of the treatment. The diet should be continued for three days after the last injection, that is, until the gonadotropin effect has worn off. The reason for this procedure is that, during the period when the hormone is effective, the slightest digression from the prescribed diet results in a marked increase of weight (far in excess of the weight of the extra food consumed) owing to the induced water retention. Patients should be warned that they cannot expect to have a normal bowel movement on their restricted diet. Under no circumstances should they be allowed to take laxatives. One stool every third day is still normal provided they drink plenty of water. If there is a longer pause, it can be corrected with a glycerin suppository. On the evening of the third day after the last injection the patient may revert to a normal diet, eating whatever he pleases. He will find his appetite conspicuously diminished. He should, however, be weighed regularly and if an increase of more than 2 pounds occurs he must skip one meal which, if omitted within forty-eight hours of the weight gain corrects the imbalance at once. In the patients who show a tendency to re-gain weight, the treatment can be repeated periodically. The method is equally effective in all

forms of obesity, even if they are very mild, regardless of the basal metabolic rate, sex, age and the status of gonadal function.

ASSOCIATED SYMPTOMATOLOGY—RESULTS OF TREATMENT

The most interesting aspect of the gonadotropin-diet treatment is the immediate and often dramatic effect it has on the associated symptomatology, which begins to improve during the first week of dieting—long before the loss of weight is such as to be mechanically significant. To some slight extent this phenomenon appears to be due to the gonadotropin as such, but it is markedly enhanced when combined with the 500-calorie diet.

Circulatory system

One of the first symptoms to disappear is breathlessness on exertion. This occurs even in patients showing myocardial damage in the electrocardiogram before treatment. In these cases it is not uncommon to find a distinct improvement in the ECG after treatment, probably due to the removal of abnormal fat from the heart muscle. It is in these cases particularly that a copious diuresis occurs during the first week, though there is no restriction in salt intake. Several cases of coronary infarction have been treated as soon as the ECG became stabilized. They too showed a further pronounced electrocardiographic improvement.

The treatment has a regulatory effect upon arterial tension. An abnormally low pressure tends to rise, and benign hypertension may be gradually reduced. At the same time high blood cholesterol readings may become normal, while the esterified fraction decreases with a corresponding increase in free cholesterol. A ratio otherwise seen only during pregnancy is often reached.

Metabolic disorders

An abnormally high level of blood uric acid, with or without manifest signs of gout, is invariably reduced. In patients who have previously suffered from gout, an acute attack sometimes occurs during the treatment. However, they then remain free of further attacks, regardless of what they eat, if the reducing regimen is continued until their weight is normal and if they do not re-gain weight. This applies only to gout associated with obesity.

Clinically the most important of the concomitant syndromes is diabetes mellitus. Obviously the diet lowers the level of blood sugar but it is a peculiar and regular feature of the method that though the diet remains unchanged, the blood sugar level continues to decrease as weight is lost. Surprisingly, this method rarely induces more than an occasional and insignificant degree of acetonuria, so that an obese diabetic can be kept comfortable and without risk on 500 calories without insulin, for several weeks. Insulin resistant cases do particularly well. The greater the degree of obesity, the better are the results. In many of these cases with blood sugar levels ranging from 200 to 300 mg. per 100 ml., the values remain within normal limits after treatment and the patients can dispense with insulin on a reasonably normal diet, as long as they do not re-gain weight. Obese diabetics with retinitis and secondary vascular changes do not do so well, probably because in them a primary organic insular deficiency predominates, whereas when these symptoms are absent the clinical picture is largely due to a

regulatory disturbance of pituitary-hypothalamic origin superimposed on an often subclinical organic insular deficiency.

Rheumatoid arthritis

In rheumatoid arthritis and in allied conditions the effect of weight reduction by the gonadotropin-diet method resembles so closely that of administering ACTH that one is forced to the conclusion that the secretion of this latter hormone is energetically stimulated. Presuming that chorionic gonadotropin is the hormone that controls the accumulation of abnormal fat and that it can be produced, as are the other gonadotropins, in the anterior pituitary lobe, clinical experience leads one to believe that the obese body's demand for gonadotropin of the chorionic type is excessive. Production is therefore stimulated to maximum capacity, apparently at the expense of other pituitary functions—among them the secretion of ACTH. When the demand for gonadotropin is adequately met by supplying it parenterally, the pituitary is suddenly relieved of this burden and resumes its other functions in full measure, thus bringing about an alleviation of all symptoms which arise as a result of secondary deficiencies of other pituitary hormones. It would seem that a mechanism of this kind would account most satisfactorily for the phenomena observed in the course of weight reduction by the gonadotropin-diet method. Obviously an increased output of ACTH achieved in this manner is preferable to its parenteral administration, because the supply is continuous and the amount produced is strictly regulated by the body's demand. Toxic symptoms, therefore, do not arise. Just as in the case of therapeutically administered ACTH there is, apart from the relief of rheumatic symptoms, a decided euphoria and a vast range of beneficial effects on disorders other than rheumatic. Moreover the effect persists after treatment, as long as weight is not re-gained. The symptomatology of peptic ulcer is dramatically relieved, nearly all allergic manifestations regress and a number of dermatoses, such as acne vulgaris, psoriasis and some eczemas are markedly improved.

The gonads

Though neither function nor presence of the gonads is necessary to bring about a weight reduction by the gonadotropin-diet method, the gonads are undoubtedly stimulated. This is possibly not a direct action of the gonadotropin but is due to the liberation of the pituitary from the burden of meeting an excessive demand for chorionic gonadotropin; thus the anterior lobe is free to resume an adequate secretion of other specific gonadotropic hormones such as FSH and LSH. In the obese female, in the absence of primary gross ovarian or uterine abnormalities, an irregular menstrual cycle becomes normal during treatment. Conception takes place during or soon after the treatment with such frequency that it is an ethical obligation to bring this to the notice of all women of child-bearing age. In both sexes there is an increase in libido in its broadest sense. There is no evidence that chorionic gonadotropin differs in its action in the male or the female. When used as a means of reducing weight in the higher age groups it has an effect similar to that of administering a combination of estrogens and methyltestosterone, provided there is a remnant of gonadal function.

Other symptoms

The characteristic "pituitary" headache of the obese disappears within a week of treatment. Loss of scalp hair is often, though not always, stopped abruptly. Brittle fingernails become less fragile. The lethargy of the obese changes to a desire for movement and the amount of sleep required is reduced.

COMMENT

There is a striking similarity between the effects of pregnancy and the effects of reducing obese patients by the gonadotropin-diet method in both sexes and at all ages. It is well known that during pregnancy all the foregoing conditions are regularly improved. It now seems probable that this is brought about by the enormous overproduction of chorionic gonadotropin during human gestation and it may be safely assumed that this hormone plays a decisive role in making just the right amount of expendable reserves available to the fetus without depleting the mother's physiologically essential deposits. Such a view would for the first time offer a satisfactory explanation for the hypersecretion of as much as 20,000 units of chorionic gonadotropin in twenty-four hours in the urine of the gravid human female. Were it not for this super-abundance of gonadotropin, it seems doubtful whether an obese mother could carry a pregnancy safely through to term. There would be continual danger of losing essential reserves and of developing exactly those conditions to which the obese are particularly prone. The fact that just these conditions hardly ever develop, and usually improve if they are present before conception, permits us to ascribe to the overproduction of chorionic gonadotropin a role of much greater importance than it has hitherto been given.

In persons not visibly afflicted with abnormal deposits of adipose tissue, the treatment (even if such persons could be maintained on a 500-calorie diet—which they cannot be) would have none of the effects described, just as small daily doses of gonadotropin without the diet are hardly effective. To achieve the results reported here it is not only necessary that the body's demand for chorionic gonadotropin be satisfied but also that the demand, which in obesity is excessive, be reduced to normal dimensions by the removal of abnormal fat.

CONCLUSIONS

It would appear that in both sexes and at all ages a small limited quantity of chorionic gonadotropin is produced, probably by the pituitary and that except in pregnancy, the production is never in excess of the demand. This small amount is necessary for the control of obesity. When either the production falls below this limit or the demand exceeds it, obesity results. Obesity can be corrected by the administration of 125 I.U. chorionic gonadotropin daily in combination with a 500-calorie diet. In the course of such treatment a wide range of associated symptoms are dramatically relieved. The method is particularly suitable for the treatment of the aged, as it imposes no hardships and is safe.

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A GERIATRIC CLINIC IN A GENERAL HOSPITAL: FIRST YEAR'S OPERATION*

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With the continuing numerical increase of elderly persons and appreciation of the scope and complexity of their needs in health care, it is recognized that a fresh approach in service to ambulatory patients is in order. Although general hospitals have significant responsibility in providing services to this group, it is generally agreed that increased benefits can be obtained by better application of existing knowledge and facilities for the purpose of helping the aged person to maintain and develop health and healthy roots in the community.

A program for comprehensive health care and rehabilitation in every-day living of elderly persons requires the integration of many professional skills and services as well as physical facilities. It is basic that such assistance should be progressive, affording a continuity of care and the assurance that these services remain available. The program should be broad and well balanced, taking into consideration the multiple etiologic factors, the current relevant findings and the corrective measures that are applicable and available. The design of this program of services for each patient must meet the necessary needs with minimum disruption of the patient's way of life. From the economic point of view such a program of help to the individual in living comfortably and productively within his community should also serve to avoid construction and maintenance of additional institutional facilities that otherwise would be required.

An effective and economically sound health program is feasible, but there must be full and discriminating use of available diagnostic and treatment facilities and skills, functioning as related units in a comprehensive scheme. Likewise, there must be a discerning appreciation of patient and family values as well as an understanding of the needs, abilities and potentials of a group that has often been deprived of respect, status, productive employment and a purpose in life.

With these in mind, a Geriatric Clinic was started in March 1954 at the Beth Israel Hospital of New York City, to effectuate a comprehensive program for team health care of the ambulatory aged through coordination of all facilities within the hospital. Another dimension was added to include coordinating procedures with community agencies so that services from both the hospital and these other facilities could be brought together to insure a maximum of needed help. The concept, organization and administration of our program will be outlined, along with some observations on its effectiveness to date. Detailed findings will follow further study and analysis at a later date.

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ORGANIZATION AND PROCEDURE

For administrative purposes, the clinic is planned and supervised by the Physician-in-charge, Psychiatrist and Director of Social Service. Administration is a joint undertaking, and the supervision of each discipline is the responsibility of its own department.

The basic diagnostic and treatment team consists of four physicians, a psychiatrist, a nurse and a full-time medical social worker. To this team are added, as needed, medical and surgical specialists, a dentist, a nutritionist, occupational and functional therapists, a speech therapist and a psychologist, according to the particular needs presented by each patient. Laboratory and x-ray facilities are brought into play when indicated.

All members of the basic team are geriatrically oriented. As part of their preparation, and aside from their interest in the program and its philosophy, they have done considerable reading, participated in planning conferences, visited cooperating agencies and studied community facilities. In this manner they have a better appreciation of the potential of the various disciplines and facilities as integrated in our holistic approach.

There are two clinic sessions each week and each sixth session is set aside for a geriatric team conference. At the latter meeting, the administrative and supervisory personnel participate, as well as such specialists as are concerned with the patients to be discussed. Diagnostic and treatment visits to all the disciplines are made on an appointment basis, except when unforeseen developments, including medical and social crises, require an unscheduled service.

Since this clinic operates as a unit of the out-patient department, applicants are admitted who are 65 years of age and over, and meet general out-patient department requirements. Some are referred from other clinics of the hospital or on discharge from our in-patient service. Others apply on their own initiative or are referred by community health and welfare agencies or private physicians.

From the beginning, the clinic had a keen appreciation of the importance of providing comprehensive quality service. This required a control of the number of patients one team unit of this kind could handle. As a result, we saw the maximum of approximately 100 patients during the first year, and each examining physician was limited to one new patient each session.

Eligibility for this clinic has not been definitely established as yet. The following are some of the current admission criteria, flexibly applied. Since the clinic is oriented to a preventive as well as a treatment program, applicants may be accepted with or without medical complaints for total medical, social and psychiatric evaluation. Those with presenting medical complaints are accepted provided they are able to travel to the clinic and there is no urgent need for active therapy, unless their treatment is being provided in another division of our out-patient service. The clinic does not accept applicants with advanced carcinoma or those who are in need of protective psychiatric facilities. Ineligible applicants are referred to other divisions within our hospital or are helped by the social worker to get to, and use other facilities in the community. Some applicants who are of borderline eligibility have been accepted in order to develop an experi-

ence in further clarifying the scope and limitation of acceptability. When the applicant has a spouse who meets eligibility requirements, joint screening is encouraged.

The role of each member of the basic team is described in the following outline. The admitting physician reviews each application along with abstracts from our existing medical and social records, as well as reports from private physicians, other hospitals and community agencies. There is also a brief screening discussion between the admitting physician and the social worker for the determination of those patients who are likely to benefit from services of this clinic.

Once the applicant has been classified as acceptable by the screening process, the social worker undertakes a psycho-social study with reference to the presenting medical picture; she assesses current personal and family relationships, social functioning, other relevant personal and social factors, and obvious or potential needs for case-work help. Concurrently, she prepares the patient (and sometimes family members) for the clinic program and procedures.

The psychiatrist assesses the personality, emotional strengths, ego-integrative capacities and their potential influence in the current picture. An attempt is made to evaluate past instinctual and ego gratifications and defenses, in order to provide sufficient gratifications to keep the patient in emotional balance.

Following these diagnostic procedures, the examining physician undertakes a total medical survey, including a complete physical examination, indicated specialty consultations, and laboratory and x-ray studies. In this investigation, he takes into account the psycho-social and the psychiatric findings. When the pertinent studies have been completed, the case is listed for conference.

A comprehensive and differential diagnosis, and a program of services and management are then outlined at a geriatric staff conference where all staff members participate along with invited specialty consultants or others who are concerned with the patient under consideration. The conference proceedings are recorded by a stenographer and are available to team members for reference and research purposes. After a thorough discussion, a total diagnosis may be established or it may be necessary for the patient to return to the examining physician, social worker or psychiatrist for further investigation before definitive conference decisions. In all events, a program of management is outlined "case-by-case," with due consideration of the patient's personal and family resources. The staff considers the indicated therapeutic facilities by the various disciplines within the hospital and the resources in the community, and selects the appropriate regimen for management.

The goals can be short, intermediate or long-range. There are frequently a number of phases in the prescribed treatment which may vary with developments under management. Extensive medical procedures may be started, with the social worker providing sustaining practical services; or counseling by her may be considered as necessary first, in preparing the patient for the medical procedure, or with family relationship problems affecting medical procedures. These approaches may be concurrent.

Thus, in the total program for the ambulatory geriatric patient, there may be

included medical and specialty follow-up, dental care, personal and family counseling, dietary instruction, physical medicine and rehabilitation, occupational therapy, prostheses and other devices, and guidance to channels for vocational retraining or protective work-shop, adequate housing or economic assistance. Several patients have been referred to our adult mental hygene clinic and are receiving psychotherapy.

The follow-up in our clinic is conducted by the members of the basic team, who are guided by the recommendations of the conference. Medical aspects are managed by the same physician throughout, and the same social worker provides case work. Thus, the patient is assured that his medical management and welfare will be taken care of by the particular professional team members who understand and know him well. Because of this relationship, the patient himself becomes an integral part of the operating team. To him, this is a welcome innovation. Except for unexpected developments which may require unscheduled visits to the clinic, the patient returns for all services, including specialty visits, on an appointment basis. When the need for general hospital in-patient care arises, the patient is admitted. When other in-patient care, not available at our hospital is indicated, the clinic arranges for such care at other appropriate places.

In the continuing care of the patient, a husband or wife and adult children are brought into a collaborating relationship with the treatment personnel. This approach helps the family members to understand the patient, his medical and social status, and his needs. Thus they are better able to work together in the interest of the patient and the family.

OBSERVATIONS

It has been generally accepted that a thorough physical examination at certain intervals is warranted, not alone for the diagnosis and treatment of presenting complaints, but also for the study of total medical status and the clarification of deviations that are sub-clinical. This is particularly true in aged patients, in whom degenerative and neoplastic processes are so insidious in development. It is important in education for health, prophylaxis, treatment and rehabilitation in every-day living. Since there is so much personal and social deprivation in this age group, it is likewise important to have a thorough psycho-social assessment, including all relevant factors of former and current psychologic, social and employment functioning, personal and family relationships, and manner of dealing with the recurring problems of daily life. These data are correlated with the medical findings. These two disciplines are then to be coordinated with psychiatric evaluation, in order to assess the impact and effect of the psychiatric status on the patient's current problem.

The present facilities and skills available in progressive out-patient departments of general hospitals are particularly suited for the implementation of such a program. Team practice of this kind under medical sponsorship is well able to evaluate, meet medical and social crises, and provide comprehensive service for health and illness. This assures the aged person of continuing responsible care as long as he remains in the community.

In a well organized program with a closely coordinated team providing multiple services, it is also necessary to be experimental and flexible, with the elder person convinced of the importance of his own role in the entire procedure. With this operational attitude, approximately 95 per cent of our patients during the first year were helped to maintain themselves comfortably and with an increasing sense of security within the community, and within their known ways of life. Of the group of 94 who have been fully processed and are under active supervision, there were 5 who were unable to continue with this program, and were helped to plan for other care. This obviously points up the positive response of our aging group to our program.

In highly developed present-day communities with a complex picture of rich resources, as well as serious gaps in necessary resources, it is important to work out good working relationships with agencies, which will result in maximum utilization of what is available for the task.

Although we have not yet established the financial cost of this type of ambulatory service, it is our impression that it compares favorably with the usual out-patient costs, achieves more positive results in the ambulatory aged group, and avoids unnecessary uprooting of individuals for undesired placements in more costly institutional facilities.

The activation of the various disciplines described for the purpose of achieving a team method to meet the needs of the enlarging aged group requires more than zealous interest, firm convictions and professional skills. The trigger mechanism requires enlightened hospital directors and professional and lay boards.

Those who have been engaged in the planning, administrative and service aspects of this program, have experienced increased conviction about the advantages of this way of caring for the older group, and have derived unusual personal and professional satisfaction.

SUMMARY

It is desirable that elderly persons continue to live in the community unless institutional care actually is required. Too often these people have sought out permanent custodial facilities because of relatively minor or transient physical or emotional disturbances, or to resolve personal, social and economic difficulties. Similarly, any type of long-term illness or handicap may drive a person into such costly facilities, even though the condition and problem in living could be handled comfortably and economically on an ambulatory basis.

A wholly integrated program in out-patient care is described in which the physical, emotional and social resources of the patient and family, the skills and facilities of a general hospital, and the general and special services of community agencies are utilized.

The design of this holistic approach is to furnish medical, psychiatric and social services coordinated to provide comprehensive diagnosis, treatment and rehabilitation.

MANAGEMENT OF CATARACT*

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Recent improvements in the management and surgical care of patients with cataract insure success in 95 per cent of the operations performed today. Mental as well as physical preparation of the patient has added much to the restoration of useful vision. Ophthalmic surgeons are better trained now and make use of new sedatives and anesthetics to obtain improved results.

Cataract may be defined as an opacity of the crystalline lens, due to an increase in water content. It has no relation to a growth on the surface or inside the eye.

THE CRYSTALLINE LENS

The crystalline lens is a clear, ovoid body suspended behind the pupil. Its primary function is to focus images on the retina in the back of the eye. The pupil plays an important part in vision and corresponds to the opening in the shutter of a camera. The lens is directly behind the pupil and is in about the same relative position as a photographic lens. The crystalline lens is flexible to a certain degree and is covered by a thin transparent membrane or capsule; it hardens and becomes less resilient with age, which explains the need for reading glasses in many older people. It is bathed by a clear fluid, the aqueous humor. This is its only source of nutrition, as there are no blood vessels or nerves supplying it directly. Any chemical derangement of the aqueous humor which will affect the crystalline lens may cause cataract formation, which explains why lens opacities develop in many patients with diabetes mellitus.

The capsule of the crystalline lens is a homogenous membrane, which is thicker on its anterior than its posterior surface. The anterior capsule is further identified by a single layer of cuboidal epithelial cells; these extend to the region of the equator where they end rather abruptly by shifting obliquely into the substance of the lens. The nuclei of these cells lose their staining reaction as they proceed inward and are incorporated in their own lens fibers. The posterior capsule continues from the equatorial region without cuboidal cells but with elongated lens fibers ending in its own substance. As the prismatic lens fibers recede from the equator toward the center, visibility is lost and a hard nucleus of the lens is formed. This is the beginning of the nuclear cataract. As age advances, it becomes more pronounced and is separated from the capsule only by a thin cortex of viable fibers. However, new fibers are formed at the equator as long as life continues.

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CATARACT AS A PART OF THE AGING PROCESS

The most common type of cataract accompanies, and seems to be a part of, the general aging process; it is referred to as *senile* cataract. The changes in the lens include hardening and enlargement of the nucleus, with separation and liquefaction of the cortical lens fibers. In the nuclear type of cataract there is often a brownish discoloration in the center of the lens with fewer changes in the periphery. In the cortical type, most of the changes take place between the capsule and the nucleus, and may assume numerous characteristics as described in ophthalmic textbooks. Subcapsular cataracts often follow exfoliation of the lens capsule. Senile cataract usually begins about the age of 50 and involves both eyes. The development may be slow or rapid and more pronounced in one eye than the other. It has been said that everyone beyond the age of 50 has cataracts in some form, but they may not mature or require operation. The alteration of the aqueous humor as age advances obviously has its effect on the nutrition of the lens and plays a great part in the development of senile cataract.

CATARACT AND GENERAL DISEASES

An example of cataract associated with general disease is that which occurs in the course of diabetes mellitus. It is possible to have cataract of the senile type in the presence of diabetes mellitus, but hyperglycemia usually hastens the development of the opacity. The changes in the lens are confined to the cortex and subcapsular layers, and very often the capsule is exfoliated and contains deposits of pigment on its surface.

Cataract may accompany tetany resulting from the removal of the parathyroids, and may be arrested by treatment with calcium and parathyroid hormone. Latent tetany is first manifested by small opaque granules deposited beneath the capsule, later invading the fissures and substance of the lens.

Other general diseases in which cataract is a common complication are: myotonic dystrophy, atopic dermatitis, and arachnodactyly.

COMPLICATED CATARACT

"Complicated cataract" is the term used to describe the type of lens opacity resulting from disease within the eye, such as iridocyclitis, glaucoma, chorioretinitis, detachment of the retina and other disorders. The changes are usually capsular at first; later the cortex and nucleus are involved. Operative results in complicated cases are usually poor and the well-trained ophthalmologist reserves surgical intervention until the last.

TREATMENT OF CATARACT

Management of cataract, once it is discovered, is most important. Certain types of cataracts never develop to maturity and do not interfere materially with vision. Surgery is not indicated in these cases. When vision is severely diminished, an operation is usually necessary. The most difficult cataract to treat successfully in the one accompanied by glaucoma. The cloudy, over-ripe lens may become swollen and aggravate the glaucoma, necessitating removal in order to relieve

the increased pressure in the eye. The final result is not always good, especially if the patient postpones the operation too long. Complicated cataracts, secondary to inflammatory processes within the eye, respond to surgery in proportion to the damage inflicted. If the retina is destroyed, little will be gained from an operation. This explains why some patients are unable to see well after a cataract is removed successfully.

THE OPERATION

Development of newer operative technics with improved safety measures have proved most satisfactory to both the patient and the ophthalmic surgeon. The intracapsular cataract extraction with a round pupil in selected cases is the ideal goal of all operators. The operation is not safe unless the lips of the operative wound are closed by sutures. Certain precautions are necessary when the sutures are placed but experienced surgeons have little difficulty at this stage of the operation.

As soon as the cataract has been delivered, the safety sutures are fixed, the operative field cleansed, and a dressing placed over the closed eye. The other eye is left open and the patient is given a small peep-hole in a double mask, or advised to keep the eye closed most of the time; this relative freedom is reassuring to the patient and often prevents serious mental reactions.

POSTOPERATIVE CARE

The dressing is changed on the second day and alternate days thereafter, until the sutures are removed on the tenth or twelfth day. The dressing may be retained a few days longer for the sake of comfort.

The patient may be permitted to get up on the second day, but if there is any indication of possible hemorrhage he should remain in bed as long as necessary. Most intraocular hemorrhages occur during the first five days after operation. Therefore, unless there is some definite urgency, the patient fares better if he remains quietly in bed for that period.

Glasses are often prescribed at the end of two weeks. Reading lenses may be ordered at the end of a month, with the understanding that they will need changing when the eye becomes more normal.

Adjustment of the patient to his new vision is helped by the explanations given by the ophthalmic surgeon. After a few weeks the patient becomes accustomed to his new sight, feels a new sense of freedom, and is usually happy.

PROBLEMS IN THE TREATMENT OF THE DIABETIC CARDIAC PATIENT

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The combination of diabetes and heart disease is common, reflecting their increased coexistence in our aging population. In a two-year period ending January 31, 1955 there were 689 admissions of patients with diabetes mellitus to Mount Carmel Mercy Hospital. Two hundred and five of these admissions (30 per cent) were of patients with heart disease in addition to diabetes. We propose to review briefly the broad principles of therapy in diabetic cardiac patients and to indicate when and how such therapy may be modified to meet the exigencies of complications. This study is an extension and revision of a previously published study of a smaller number of patients (1).

Arteriosclerotic cardiovascular disorders develop at earlier ages and are more frequent and more severe in diabetics than in non-diabetics; also, their incidence in females is greatly increased in the presence of diabetes. Hypertension is a common concomitant of diabetes mellitus, even in the absence of intercapillary glomerulosclerosis. Arteriosclerosis and hypertension, singly or in combination, were the causes of the cardiac lesions in 98 per cent of our series.

The pathologic changes in arteriosclerotic heart disease in diabetics differ only in degree from those in non-diabetics, and we know just as little about the pathogenesis of arteriosclerosis in diabetics as in non-diabetics. In diabetics, the metabolic substrate (elevated levels of blood sugar, cholesterol and lipids) and the overweight and hypertension so often seen, predispose to atheromatous changes. However, there seems to be no proportional relationship between the degree of coronary sclerosis and the *severity* of the diabetes, although there may be some relationship to its *duration*.

CLINICAL DATA

During the two-year period ending January 31, 1955, 174 patients with diabetes and heart disease were hospitalized, some being admitted more than once for a total of 205 admissions. Pertinent clinical and etiologic data are summarized in Table 1. The diabetic status ranged from asymptomatic hyperglycemia to severe ketosis, and the cardiac status from asymptomatic electrocardiographic or x-ray abnormalities to massive myocardial infarction with shock, pulmonary edema, congestive failure and arrhythmias. Ordinarily, the management of a patient with diabetes and heart disease poses no unusual problems, as exemplified by the fact that in 151 patients (87 per cent) the diabetes was either under control or else hyperglycemia and ketonuria were readily controlled with appropriate measures. In the remaining 23 patients (13 per cent), the ketosis was more severe, more prolonged, and less responsive to therapy. In 7 of these patients, the outlook appeared ominous because of the degree of diabetic break-

TABLE 1. *Etiologic Data*

Number of patients			174
Number of admissions			205
Sex: Male			80
Female			94
Age: Male	Range—37 to 86 years	Average	60
Female	Range—42 to 89 years	Average	64
Reason for admission:			
Management of diabetes			11
Cardiac complaints			124
Coincidental problems (*e.g.*, surgical, traumatic or cerebrovascular emergencies, infections, or peripheral arteriosclerosis)			70
Etiologic categories of heart disease and major manifestations:			
1. Bacterial endocarditis, acute			1
2. Rheumatic heart disease			2
Asymptomatic		1	
Congestive failure		1	
3. Hypertensive heart disease			38
Asymptomatic		26	
Congestive failure		12	
4. Hypertensive and arteriosclerotic heart disease			31
Asymptomatic		7	
Anginal syndrome		5	
Acute myocardial infarction		5	
Congestive failure		14	
5. Arteriosclerotic heart disease			102
Asymptomatic (including old infarctions)		23	
Anginal syndrome		13	
Acute myocardial infarction		37	
Congestive failure		28	
Paroxysmal ventricular tachycardia		1	

down. These 23 instances of severe ketosis were associated with myocardial infarction in 10 patients, congestive failure in 5, and other diseases such as infection or cerebrovascular accidents in 8. It is in these severely ketotic patients that therapeutic dilemmas are apt to arise, since the administration of fluids, electrolytes and insulin indicated for the diabetes may be contraindicated by the cardiac status.

Forty of the 174 patients in this series died. The causes of death were as follows:

Myocardial infarction	14 cases
Congestive failure	13 cases
Cerebrovascular accidents	7 cases
Uremia	2 cases
Gangrene, pulmonary embolus, pneumonia, bacterial endocarditis	1 each

Diabetic ketosis or complicating electrolyte disturbances did not directly account for any of the deaths in this series.

HYPOGLYCEMIA AND CARDIAC DISTURBANCES

Insulin, indispensable in the treatment of diabetes, has potent cardiovascular effects when given in dosage capable of inducing hypoglycemia. Insulin overdosage reportedly has induced angina, acute pulmonary edema, myocardial infarction, and congestive heart failure. Insulin hypoglycemia may cause tachycardia, elevation of systolic arterial pressure and of venous pressure, increase in stroke volume, cardiac output and cardiac work, arrhythmias, and ST-T changes in the electrocardiogram. These cardiovascular responses to hypoglycemia are reminiscent of the effects of adrenaline, and when the pallor, sweating and apprehension which occur in hypoglycemia are considered, the similarity to adrenaline effects becomes more marked.

Since myocardial glycogen appears to be fairly well cushioned against depletion by transient hypoglycemia, at least in the presence of an adequate supply of oxygen, it has been suggested that the cardiovascular manifestations of insulin hypoglycemia are mediated by adrenergic discharge (from the adrenal medulla and cardiac sympathetic nerves) and not by any direct cardiac action of insulin or hypoglycemia.

In the presence of diminished coronary flow or decreased cardiac reserve from any cause, these adrenaline-like effects of excessive insulin dosage become critically important. The tachycardia or arrhythmias, elevated venous pressure, and increased cardiac work precipitated by hypoglycemia may lead to decompensation in a damaged heart. Hyperglycemia is preferable to hypoglycemia in these patients and one cannot entirely eliminate the possibility that *mild* hyperglycemia may aid myocardial nutrition when coronary flow is impaired.

ANGINAL SYNDROME

Although our series includes only 18 patients hospitalized with angina pectoris and diabetes, this situation is the most frequent in office practice. We have noted that hypoglycemia may precipitate episodes of anginal pain. On the other hand, poor diabetic control with persistent hyperglycemia, glycosuria, and the accompanying weakness and dehydration may decrease myocardial reserve in the heart damaged by coronary artery disease and/or hypertension. Such hearts may not be able to meet ordinary demands, and angina or congestive failure may result.

The diabetic cardiac who is underweight at the onset of difficulties is more likely to have a more severe form of diabetes and more frequent anginal episodes than the obese patient. Such underweight patients must be particularly protected against hypoglycemic episodes because of the deleterious cardiovascular effects already described. Rigid standards of diabetic control are best relaxed in this group of patients and we should be satisfied to maintain their fasting blood sugar levels between 110 and 150 mg. per 100 ml. Occasional mild glycosuria in these patients is reassuring rather than disturbing.

The underweight diabetic is best treated with a high carbohydrate diet (175–250 Gm. daily), whether or not insulin is necessary. In new patients, we have found that the amount of sugar excreted in the urine in 24-hour periods is a good index of the current severity of the diabetes and a good guide to initial insulin dosage. In the absence of ketosis or other acute complications, there should be a trial of diet without insulin at first, if glycosuria does not exceed 25–35 Gm. in twenty-four hours. With greater urinary loss of glucose, insulin should be started concurrently with the prescribed diet. Usually the choice is protamine zinc insulin in an initial dosage of 1 unit for every 1.5–2.0 Gm. of urinary glucose in the 24-hour specimen. In order to reduce the likelihood of nocturnal insulin reactions, the insulin may be taken at bedtime whenever feasible. If hypoglycemic reactions develop, they are then likely to occur the next morning when they can be readily recognized and promptly treated by the patient. The high carbohydrate diet and the nocturnal administration of insulin are probably useful measures in all older diabetics, even in the absence of clinically demonstrable cardiac impairment, because they tend to prevent damage from precipitous drops in the blood sugar level due to too much insulin or insufficient carbohydrate intake.

In the obese diabetic with angina, weight reduction via caloric restriction usually improves both the diabetes and the cardiac status. Angina may disappear when a more ideal weight is approached, since the load on the heart is lessened. Hyperglycemia and glycosuria may subside with weight reduction and the only evidence of diabetes which remains may be an impaired carbohydrate tolerance curve; indeed, the tolerance curve not infrequently becomes normal after adequate weight reduction in the obese diabetic and the predilection toward diabetes may be evident only in impairment of glucose tolerance after orally administered cortisone, as recently reported by Fajans and Conn (2). Although the beneficial effect of caloric restriction in the obese diabetic is generally known, it is too often forgotten or neglected. In the obese diabetic cardiac patient, since weight reduction brings about added dividends in improvement of the cardiac symptoms, it should be the first principle of therapy. Naturally, the usual therapeutic measures for angina are instituted at the same time, *e.g.*, nitroglycerine, necessary restrictions of physical activity, and avoidance of precipitating factors.

MYOCARDIAL INFARCTION

In this group of 174 diabetic cardiac patients, 42 were admitted with acute myocardial infarction. Fourteen of these 42 patients died—an uncorrected mortality rate of 33 per cent. During the same two-year period covered by our survey, 669 *non-diabetics* with acute myocardial infarction were admitted, of whom 149 or 22.3 per cent died. Thus, the acute infarct in the diabetic carries a higher mortality risk than in the non-diabetic.

Severe ketosis was associated with the infarction in 10 patients. It was sometimes difficult to determine whether the infarction precipitated the ketosis or vice versa, since the shock, dehydration, hypovolemia and hemoconcentration occurring in severe diabetic ketosis predispose to thrombosis in atherosclerotic

coronary arteries. The severity and extent of the infarct, the state of diabetic control, and the presence or absence of complications are the determining factors in the degree of metabolic derangement following infarction. The infarction may cause no discernible impairment of control in a mild or moderate diabetic; or ketosis and coma may develop rapidly following coronary occlusion.

Myocardial infarction is often the first manifestation of heart disease and in a diabetic it may be obscured by the severity of the metabolic reaction. In 1 case in this series, the sudden development of ketosis in a previously stabilized diabetic with no cardiac symptoms led to a search for the cause and a clinically silent infarct was found electrocardiographically.

It is probably wise to make a fasting blood sugar determination in all patients with myocardial infarction, since in some elderly diabetic patients a high renal threshold may permit fairly marked hyperglycemia without glycosuria.

The diagnosis of myocardial infarction associated with diabetic ketosis may be difficult. The electrocardiogram may be normal or may show non-diagnostic changes in the first few hours or days after coronary occlusion; and it may be abnormal in diabetic ketosis not associated with heart disease. This latter eventuality may be observed during recovery from severe acidosis under two circumstances: 1) over-enthusiastic administration of insulin with subsequent hypoglycemia and ECG changes secondary to the low blood sugar level, or 2) hypopotassemia, which may be reflected in conduction disturbances, ST and T wave changes, and fusion of T and U waves. The altered ST and T waves in either case may resemble those of myocardial ischemia but they rapidly return to normal as the metabolic disturbance is corrected.

The electrocardiogram may be abnormal in diabetics in the absence of heart disease. Similarly, myocardial infarction may cause disturbances in carbohydrate metabolism in the absence of diabetes. Mild glycosuria and hyperglycemia (fasting blood sugar level of 120–150 mg. per 100 ml., or higher) are commonly seen during the first day after coronary occlusion in patients with no past history or family history of diabetes. Acetonuria may be evident if the infarction is accompanied by vomiting. Glucose tolerance curves are usually normal subsequently, although impaired carbohydrate tolerance may be present for a few weeks after the infarction, particularly in the younger patients with coronary thrombosis. These temporary disturbances in carbohydrate metabolism are variously interpreted and may reflect varied etiology. Some of these patients are probably preclinical diabetics whose homeostatic defenses have given way temporarily as a result of the heart damage. In others, the adrenals are believed to increase their output of epinephrine and glucocorticoids, stimulated by the intense stress of the infarction; the epinephrine increases hepatic glycogenolysis and the glucocorticoids stimulate gluconeogenesis. It has recently been reported (3) that hyperglycemia is an indication of more severe involvement, is seen usually in patients with profound shock, and is associated with central liver-cell necrosis.

The treatment of the patient with myocardial infarction and diabetic ketosis depends upon which factor is more critical at the time, and may vary from hour

to hour. Treatment of the infarction consists basically of rest, relief of pain, and reassurance, plus oxygen, sedatives, antihypotensive agents, and anticoagulants when indicated. Morphine has a slight antidiuretic effect and, in some patients, a tendency to induce vomiting. These effects are obviously undesirable in cardiac patients, especially in those with diabetic acidosis. The addition of atropine to the morphine or the use of smaller doses of morphine (8 mg.) at more frequent intervals, intravenously if warranted, may eliminate the emetic tendency; or other narcotics may be used. The hyperglycemic effect of nor-epinephrine usually is not of sufficient degree to contraindicate its use in diabetics.

The depletion of fluids and salt in acidosis leads to dehydration, hemoconcentration, and deficiency of base for excretion of ketone bodies. Fluids and electrolytes, as well as insulin, are urgently indicated but the damaged myocardium may be unable to tolerate the increased circulatory load. Without going into detail regarding the usual treatment of diabetic ketosis or coma, it should be emphasized that in these situations special nurses are very helpful; an indwelling catheter, despite the risk of pyelitis, is almost a necessity for collecting frequent urine specimens for analysis for sugar and ketones; and determinations of blood sugar, CO_2 combining power, and serum sodium, chloride and potassium are highly desirable indicators of the effectiveness of treatment. A flame photometer is a valuable instrument in these cases because it permits fairly rapid recognition of electrolyte disturbances which can seriously compromise recovery from ketosis. We feel that the electrocardiogram is only a rough and generally unreliable guide to serum potassium levels, except in extreme cases, and its value in these situations is further diminished by the changes resulting from the infarction.

Shock may be due to the infarction or to the ketosis or both. Severe peripheral circulatory collapse interferes with the absorption of subcutaneously administered insulin, and intravenous insulin is therefore advisable in the early stages of treatment of severe ketosis with shock. Similarly, hypodermoclyses of fluids and electrolytes may not be absorbed effectively. This is unfortunate, because ordinarily the slower rate of absorption of subcutaneous fluids tends to prevent overburdening the circulation, a dangerous possibility with an infarcted myocardium. In a conscious patient, fluids and salt can be taken orally, as well as alkali in the form of bicarbonate and potassium salts in orange juice when necessary. If coma or vomiting prevent oral rehydration, and therefore intravenous fluids must be used vigorously, the neck veins should be observed carefully for increasing distention and the lungs examined often for basal moist rales. Frequent measurements of the venous pressure will also help in the early recognition of impending failure.

In diabetic ketosis not complicated by heart disease, it is customary at our hospital to use insulin and saline without glucose in the first six to eight hours of therapy. Essentially this is a compromise between the ardent protagonists of the immediate use of glucose in saline, plus insulin (who argue that under this regimen the blood ketones are reduced more rapidly) and the equally ardent antagonists (who insist that early glucose administration may increase water

and potassium losses and prolong the hyperglycemic phase). However, in the patient with myocardial infarction and diabetic ketosis, the administration of glucose from the start of treatment is safer, because it lessens the likelihood of sudden hypoglycemia. In severe ketosis, insulin resistance (or inhibition of insulin action) is common; but with beginning recovery there may be precipitous drops in the blood sugar level in response to doses of insulin which were previously ineffective.

Recent investigations of fructose metabolism in diabetes suggest that fructose decreases ketone body production, is readily metabolized to lactose and pyruvate, can be utilized without insulin, and causes less hyperglycemia, glycosuria and water loss than does glucose. Although our series furnishes no data in this matter, it would seen that the use of fructose may be helpful in the early treatment of diabetic emergencies. The fructose may be administered intravenously in 2.5 per cent to 10 per cent solution in normal or half-normal saline.

Acute cardiac complications during recovery from diabetic acidosis may be due to insufficient potassium, excessive fluids and salt, excessive insulin—conditions which are usually reversible—or to extension of the infarction. The early administration of glucose is not likely to lead to clinically significant hypopotassemia, provided the physician is alert to the possibility and supplies potassium salts orally (or intravenously, if necessary), beginning about six hours after the start of treatment if urinary output is satisfactory. Hypopotassemia tends to develop during apparent recovery from acidosis and may cause hypotension, tachycardia, cardiac dilatation with gallop rhythm and murmurs, plus the electrocardiographic abnormalities previously mentioned. Over-enthusiastic treatment with fluids and salt may lead to acute pulmonary edema during this period of apparent recovery from acidosis. Also, in this same period, insulin hypoglycemia may develop, with its attendant cardiovascular manifestations.

In summary, then, the successful treatment of a diabetic patient with myocardial infarction is dependent upon continuous observation of the patient, recognition that the myocardial reserve must guide the rapidity of administration of water and salt, and alertness to the possibility of insulin excess as well as potassium deficit.

CONGESTIVE HEART FAILURE

In 55 patients (32 per cent), congestive heart failure was the major manifestation of cardiac insufficiency and caused 13 deaths. Cases of pulmonary edema were included in this group. The congestive failure was associated with rheumatic heart disease in 1 case, hypertensive or hypertensive and arteriosclerotic heart disease in 26, and arteriosclerotic heart disease in 28.

The management of diabetes is complicated by congestive failure because of the increased metabolism in failure, the gastrointestinal disturbances (anorexia, nausea, vomiting, bowel dysfunction) associated with visceral congestion, and the problems of fluid and electrolyte balance in relation to digitalis and diuretic administration. These problems are magnified in the presence of acidosis.

Diuretics increase the excretion of sodium, chloride, potassium and water.

Thoracentesis or paracentesis results in loss of electrolytes by way of the fluid removed. To avoid precipitating hyponatremia or hypopotassemia in patients with diabetic acidosis and right-sided heart failure, it is better to direct initial therapy toward clearing up the acidosis and subsequently to use diuretics and/or digitalis as necessary in order to eliminate the increased peripheral fluid. When the failure is manifested mainly by severe pulmonary edema, there should be no temporizing and diuretics should be given early if glycosides, oxygen, morphine and aminophylline are not successful in relieving the congestion. Hypertonic glucose balanced by insulin may be a helpful diuretic in these situations. Aminophylline given intravenously about half an hour after an injection of a mercurial diuretic will result in sharp potentiation of the diuretic effect.

The principles of treatment of diabetic acidosis and of congestive failure seem to be diametrically opposed, as far as electrolytes and intravenous fluids are concerned. However, the difficulties can be resolved successfully if therapy is varied according to the needs of the moment and if we are alert to the possible implications of the therapy employed. For example, let it be assumed that in a digitalized patient with diabetic ketosis pulmonary edema develops as a result of an intolerable increase in the circulatory load resulting from intravenous fluids and salt. It is urgent that the pulmonary edema be relieved. Therefore, we start oxygen, put cuffs on the arms and thighs, and give atropine, a small dose of morphine if the patient is conscious and apprehensive, and 0.5 Gm. of aminophylline in 50 cc. of 50 per cent glucose intravenously very slowly. If the pulmonary edema persists, more vigorous diuresis is necessary. At this point, while injecting a mercurial diuretic, the possible eventualities must be considered. With vigorous diuresis, more potassium will be lost and hypopotassemia may develop. At least part of the digitalis toxicity which may follow diuresis appears to be due to potassium loss rather than to mobilization of digitalis from body fluids, and may be associated with decreased myocardial potassium content. We must then be prepared to administer potassium to counteract the digitalis toxicity as well as the other manifestations of hypopotassemia. A flame photometer is helpful for rapid determination of the concentration of serum electrolytes but it is not essential. Anticipation of the complications that may arise is much more important.

The important role that the vitamin B complex plays in intermediary carbohydrate metabolism suggests that vitamin B, especially thiamine, should be added to the therapy of diabetics when there is failure to provide for excessive loss of water-soluble vitamins in the urine and for intensified demand resulting from increased metabolism. In some patients congestive heart failure is resistant to treatment, due to unsuspected concomitant thiamine deficiency.

SUMMARY

1. One hundred and seventy-four patients with diabetes and heart disease hospitalized in a two-year period are reviewed briefly as a background for a discussion of the problems which may arise in diabetic patients with angina, myocardial infarction and congestive failure.

2. In most of the patients, the co-existence of the two diseases did not seriously complicate the treatment of either. In a small group of patients (13 per cent), including 10 with myocardial infarction and 5 with congestive failure, the breakdown of diabetic control was severe and posed major problems in therapy.

3. None of the 40 deaths in this series was attributable to diabetic coma or complicating electrolyte imbalance.

4. Awareness of the possible complications arising during treatment and readiness to adjust therapy to meet the exigencies of the moment are the most important principles in management.

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THE USE OF A CARBONIC ANHYDRASE INHIBITOR IN THE TREATMENT OF HYPERKALIEMIA*

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In chronic renal disease, in addition to the difficulties that may arise through metabolic derangements associated with the retention of nitrogenous and other end-products of catabolism, blood electrolyte concentrations are also often disturbed as a result of derangement of renal tubular function.

In some types of chronic renal disease the urinary potassium loss is either greater than normal, or not significantly impaired. In these cases the correction of such fluid and electrolyte deficits as may be present (particularly the replacement of sodium and chloride) often serves to correct the renal acidosis, and may correct any tendency to hyperkaliemia. In the Fanconi type of renal tubular derangement, there is considerable potassium loss through the tubules in addition to marked bicarbonate loss. In such cases, although hyperkaliemia may be an early immediate problem, the administration of sodium lactate solution will usually not only correct the renal acidosis but also the hyperkaliemia. In fact, potassium loss may be so increased by this form of treatment that hypopotassemia results, unless the precaution is taken of giving potassium along with the sodium lactate solution (1).

In some of the other forms of chronic renal disease represented by the clinical diagnoses of chronic glomerulo-nephritis and chronic pyelonephritis, notwithstanding efforts to correct electrolyte deficits and to hydrate the patient, serum potassium levels may continue to rise despite increasing urinary output, or may remain at clinically significant elevations. This condition increases the patient's distress, because of the additional deleterious effects that excess serum potassium may induce.

Forcing fluids in such instances may increase urine volume but this will not in itself increase the loss of potassium. Osmotic diuretic agents, acidifying agents, the xanthines and mercurials will not prove helpful under these circumstances. In fact, mercurials, except in instances of sodium depletion, appear to inhibit the excretion of the amount of potassium that the tubular cells would usually be capable of secreting (2).

A carbonic anhydrase inhibitor, acetazoleamide (Diamox), has been observed in laboratory and clinical subjects to cause a copious loss of sodium, potassium, bicarbonate and water through the mechanism of blocking the formation of carbonic acid (H_2CO_3) in the renal tubular cells. This interference results in a

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loss of sodium, because of a lack of available H^+ ions to substitute in the tubule for one of the Na^+ ions of the disodium salts. This diminished concentration of H^+ ions permits more potassium loss from the cells, as apparently potassium transfer from the intracellular position in the cells of the renal tubules into the lumen of the renal tubules occurs by the same pathway as that of H^+ ion secretion. Thus potassium transfer is not competitively inhibited by the H^+ ions when the carbonic anhydrase enzyme system is blocked temporarily by agents such as acetazoleamide, and increased amounts appear in the renal tubules and urine.

CLINICAL MATERIAL

We have studied the effects of a carbonic anhydrase inhibitor in 7 patients with chronic renal disease who had elevated serum potassium levels. These levels did not fall with the usual measures employed in the management of such patients, even though adequate urinary volumes were established and maintained after adequate hydration and continuing attention to proper fluid and electrolyte balances.

Dialysis by gastrointestinal and the peritoneal routes was not considered advisable in view of the age and/or debility of these patients, and also because of the recognized chronicity of the disease processes. As an artificial kidney apparatus was not available, we decided to try the use of Diamox[1], a carbonic anhydrase inhibitor, in order to observe its effects on urinary potassium excretion in chronic renal disease processes.

CASE REPORTS

Case 1

I. J. (R. Hosp. # 40500), a 41-year-old colored man, was admitted to the Medical Service, October 16, 1953, with a diagnosis of chronic pyelonephritis. Supportive measures were directed toward the control of his renal infection, and a urinary volume of 2,500 cc. per twenty-four hours was sustained with a fluid intake of between 3,000 and 4,000 cc. per day. In spite of this, there was a continued elevation of the serum potassium level in the range of 6.5 to 6.8 milliequivalents per liter. In an effort to reduce the serum potassium level, Diamox was begun on the twelfth hospital day in a dosage of 500 milligrams daily, and continued for seven days. During this period of therapy the serum potassium level was reduced to 5 milliequivalents per liter. A fall in the CO^2 combining power occurred on the fourth day of Diamox administration, but was corrected promptly by the administration of 400 cc. of molar sodium R-lactate solution orally over a 24-hour period. In Figure 1 it may be seen that the serum potassium level fell prior to the administration of the sodium lactate solution to this patient. Diuresis and a weight loss of 10 pounds occurred during the period of treatment with Diamox. The patient was discharged on the thirty-first day of hospitalization and has since been observed at intervals in the out-patient clinic.

Case 2

R. S. R. (R. Hosp. # A28165), a 75-year-old white male, was admitted on October 1, 1953 because of symptoms of cholelithiasis with continuing nausea. On examination he was found to be mildly dehydrated, and to have renal acidosis. The blood urea nitrogen level (BUN)

[1] Diamox used in this study was supplied for this purpose by The Lederle Laboratories Division of The American Cyanamide Company.

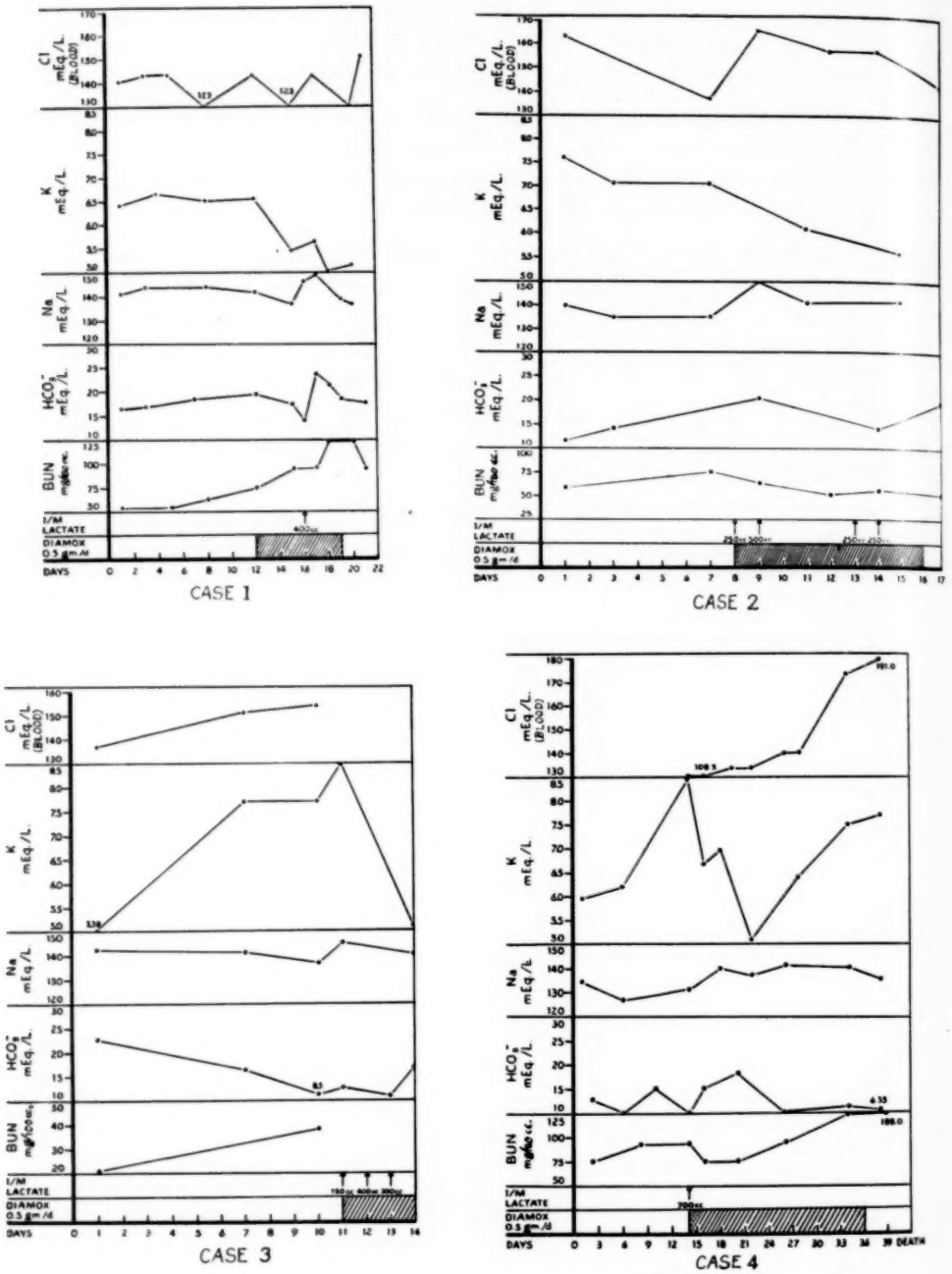

Fig. 1. Biochemical findings in serum of Cases 1–4

was elevated. The past history and the urinary findings were consistent with a diagnosis of chronic glomerulonephritis. Treatment consisted of a reduced protein intake, a low-potassium diet, intravenous infusion of glucose solutions and insulin, and the maintenance of a fluid intake in the range of 3,000 cc. per day, with a urinary output of 1,500 cc. per day. This resulted in some improvement, but as may be seen in Figure 1, there was only a slight

drop in the serum potassium level. On the eighth day of hospitalization, Diamox in a dosage of 500 milligrams daily was started and continued for the next eight days. There was a drop in the serum potassium concentration from a level of 7.2 to a level of 5.6 milliequivalents per liter on the fifteenth hospital day—the seventh day of Diamox administration. A reduction of the BUN level also occurred during this time. Molar sodium R-lactate solution was given orally at intervals to correct decreases in the CO_2 combining power and lowering of serum sodium concentration. The patient was improved enough to be discharged from the hospital on the ninth day after beginning Diamox therapy. A follow-up letter from his family physician stated that the patient subsequently died of renal failure about two months after discharge from the hospital. No weight loss was observed and there was no evident edema (except of the face) in this patient during the period of hospitalization.

Case 3

J. B. (R. Hosp. #13934), a 58-year-old colored man, was admitted to the hospital on the Medical Service, November 29, 1953, with a diagnosis of hypertensive cardiovascular disease and congestive heart failure. Bed rest, mercurial diuretics and digitalis were utilized to correct the congestive failure. Prompt diuresis and a loss of 18 pounds of edema fluid occurred during the first ten days of hospitalization. There was some elevation of the BUN level, a decrease of the CO_2 combining power, and marked elevation of the serum potassium level during the period of diuresis. Oral molar sodium lactate solution was begun on the eleventh day of hospitalization and continued daily for the next three days. At the same time a dose of 500 milligrams of Diamox was begun and continued over the next seven days. As may be seen in Figure 1, there was a prompt fall in serum potassium concentration from a level of 8.5 to a level of 5.0 milliequivalents per liter. The patient was improved enough to be discharged on the twentieth hospital day. Various studies, including that of the urinary sediment, indicated that he had some degree of chronic pyelonephritis as a complicating factor in his primary disease state of hypertensive cardiovascular disease. The pyelonephritis apparently occurred as a result of a previous operation on the lower urinary tract for carcinoma of the glans penis. The patient continued to get along reasonably well after discharge from the hospital, until September 1954, when hospitalization was again necessary for cardiac failure. Death occurred during this admission and at autopsy, in addition to confirmation of the diagnosis of hypertensive cardiovascular disease with myocardial injury and fibrosis, the diagnosis of chronic pyelonephritis was also confirmed.

Case 4

E. B. (R. Hosp. #A28509), a 58-year-old colored female, was admitted to the Medical Service on January 14, 1954, because of diabetes mellitus with acidosis due to the Kimmelstiel-Wilson syndrome. She was acidotic, edematous, and in a state of cardiac failure. Although, serum potassium concentration was reduced temporarily by the use of Diamox in this patient (Fig. 1) from a level of 8.5 to a level of 5.0 milliequivalents per liter, the state of hyperkaliemia was only temporarily controlled by this measure and the clinical course of her illness was progressively worse; renal acidosis increased, despite various supportive measures. Death occurred on the thirty-ninth day of her hospital stay. A 6-pound weight loss was temporarily achieved through diuresis as a result of Diamox administration, but it was subsequently superseded by a weight gain of 10 pounds and an increase in visible edema.

Case 5

L. B. (R. Hosp. #A4275), a 52-year-old colored man, was admitted to the Medical Service on October 30, 1953 because of congestive heart failure due to hypertensive cardiovascular disease. There was also a subsequent diagnosis of chronic pyelonephritis, with a urethral stricture. In intravenous pyelograms, the left kidney was not visualized. Retrograde pyelograms revealed reduplication of the left kidney; no obstructive lesion was evident.

With rest, digitalis, ammonium chloride in a dosage of 2 grams daily, and a mercurial diuretic (Mercuhydrin) in daily dosage of 2 cc. intramuscularly, the status of his cardiac failure was improved, but during this period of time there was a rise in blood urea nitrogen from a level of 28 mg. to a level of 54 mg. per 100 cc., with a fall in serum sodium concentration to 130.5 milliequivalents per liter and rise in serum potassium concentration to 6.67 milliequivalents per liter. Whole blood chlorides rose from a level of 430 milligrams to a level of 500 mg. per 100 cc. Diamox in a dosage of 500 mg. daily was administered for the next five days. There was a drop in serum potassium from a level of 6.67 milliequivalents to a level 4.9 milliequivalents per liter on the fourth day after beginning administration of this drug. Mercurials and ammonium chloride were discontinued forty-eight hours prior to beginning Diamox.

The patient showed some temporary improvement; then his cardiac status became worse and he died on the twenty-eighth day of hospitalization, after experiencing several pulmonary infarctions.

No further evidence of electrolyte imbalance or increase in serum potassium concentration was observed during the latter part of his hospital course, although further weight loss and diuresis were observed in the course of treatment of the congestive heart failure. His weight on admission was 124 pounds and at the time of death was 95 pounds.

Case 6

S. S. (R. Hosp. #83163), a 40-year-old colored woman, was admitted to the Medical Service on October 12, 1954, with symptoms of cerebral thrombosis and hypertensive cardiovascular disease secondary to chronic pyelonephritis. The blood urea nitrogen was elevated to a level of 54 mg. per 100 cc., and CO_2 combining power was reduced to 19 volumes per cent. The concentration of serum sodium was 151 milliequivalents per liter and of serum potassium, 7.28 milliequivalents per liter. Despite a 3,500-cc. fluid intake daily and a urinary output in the range of 1,800 cc., the serum potassium level remained elevated at 7 milliequivalents per liter. The patient received 1,000 cc. of molar sodium R-lactate on one occasion and daily infusions of 1,000 cc. of physiologic sodium chloride solution plus 1,000 cc. of 5 per cent dextrose in distilled water over a ten-day period, in addition to such orally administered fluid as could be taken by the patient. The serum sodium level rose from 286 milligrams per 100 cc. (124.3 mEq. per liter) to 308 milligrams per 100 cc. (133.9 mEq. per liter). During this same period serum potassium levels fell from 28.9 milligrams per 100 cc. (7.41 mEq. per liter) to 24.4 milligrams per 100 cc. (6.25 mEq. per liter) and remained at this level despite continuation of a fluid intake of 2,500 to 3,000 cc. and an average urine volume of 2,000 cc. per twenty-four hours. At this time a 24-hour urine sample was collected. This showed a potassium excretion of only 0.4 gram in twenty-four hours. The day following this determination, a dose of 500 mg. of Diamox was given intravenously. A second 24-hour collection of urine was then made. A total of 4.3 grams of potassium was recovered in this second collection, and there was a drop in the serum potassium level from 6.25 milliequivalents to 5.1 milliequivalents per liter (24.4 milligrams per 100 cc. to 19.6 milligrams per 100 cc.) in twenty-four hours. There was no significant change in the levels of whole blood chlorides or serum sodium during this interval.

Case 7

W. H. (R. Hosp. #A42314), a 66-year-old colored man, was admitted to the Urological Service of the hospital on January 28, 1955 with a diagnosis of hypertensive cardiovascular disease and evidence of prostatic disease with obstruction. After perineal prostatectomy, a medical consultation was requested because of the problem of increasing uremia. On February 13, 1955, fluid intake was forced and parenteral fluids in the form of 5 per cent dextrose in water, 5 per cent glucose in saline and 1/6 molar sodium R-lactate were employed to supplement the oral intake. Between February 15 and February 24 the fluid intake was maintained by oral and parenteral measures in a range between 3,000 and 5,000 cc. per day.

TABLE 1. *Serial Biochemical Studies in Serum of Case 7*
(Fall of serum potassium level after administration of Diamox.)

Date 19[illegible]	BUN (mg./100 cc.)	Na (mg./100 cc.)	K (mg./100 cc.)	Cl(blood) (mg./100 cc.)	CO_2 comb. power (vol. %)	Remarks
Jan. 26	21					Preop.
Feb. 13	63					3rd postop. day
Feb. 15	83	312	23.2	430	46	Avg. fluid intake 2,500 cc./24 hrs.
						Avg. urine volume 2,000 cc./24 hrs.
Feb. 20	30					Fluids forced.
						Avg. fluid intake 4,000 cc./24 hrs.
Feb. 23		312	30.4	480	62	Avg. urine volume 2,500 cc./24 hrs.
						Diamox, 500 mg. (1st dose)
Feb. 24	42	324	28.1			Diamox, 500 mg. (2nd dose)
Mar. 1		316	23.2			
Mar. 4	48	323	26.4		56	

Urinary volume was maintained at a level of from 2,000 to 3,500 cc. per day. Despite the improvement of urinary output and a subsequent fall in the BUN level, the concentration of serum potassium remained elevated (Table 1). On February 23 and again on February 24 Diamox was given in dosage of 500 milligrams each day. As may be seen from Table 1, a prompt fall in the serum potassium level occurred after the administration of 500 milligrams of Diamox daily on two successive days. Following further improvement the patient was discharged from the hospital on March 7, 1955.

COMMENT

Administration of acetazoleamide to increase the loss of potassium from the body through urinary excretion can be utilized in patients who have chronic renal disease, as shown by the results in the 7 patients whose clinical courses have been presented. With repeated administration of this drug, precautions must be taken to prevent an increase in metabolic acidosis. However, by following the levels of serum sodium, blood chlorides, and CO_2 combining power in these patients appropriate corrective therapy may be promptly and easily instituted. In instances in which adequate urinary output can be maintained, a carbonic anhydrase inhibitor is a valuable adjunctive agent in managing a patient with hyperkaliemia, combined with other measures currently in use. Such measures consist of the judicious correction of dehydration and of electrolyte imbalances, the parenteral administration of glucose and insulin, and the use of various forms of dialysis by way of the intestinal tract, the peritoneal cavity or an artificial kidney (4).

SUMMARY

A review is presented of the basic concepts of the action of inhibitors of the carbonic anhydrase system and the relation of this system to potassium excretion from the renal tubular cells.

Seven case reports are presented to indicate the therapeutic effectiveness of a carbonic anhydrase inhibitor (acetazoleamide) as an aid in the management of patients with chronic renal disease and an increased level of serum potassium.

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THE PREFERENCE FOR STREPTODUOCIN IN THE TREATMENT OF TUBERCULOSIS OF THE AGING*

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Considerable optimism (1) regarding tuberculosis has been generated in the public mind as the result of new chemotherapeutic agents and the rapidly falling death rate, but those of us close to the tuberculosis problem believe that the optimistic outlook is not entirely warranted. Although it is true that the death rate is falling rapidly, with possibly fewer new cases being found, the prevalence or total number of cases of tuberculosis in the community is actually greater, and in the older age group.

The increased prevalence of tuberculosis is due to the higher survival rate of the treated patient compared with that in the prechemotherapeutic era. With mortality having decreased from an annual death rate of about 30 per cent of the number of yearly admissions to less than 5 per cent, the survivors are necessarily older—my average patient being 52 years of age.

We are not unusual in this respect. For example, Arkansas, as of January 1, 1953, reported that in 52 per cent of its cases the patients were over 45, and New York State (exclusive of New York City) reported 45 per cent in this age category. However, many physicians still have the erroneous impression that tuberculosis is rare among older people. When tuberculosis is discovered in this group, the patient should not be sentenced to custodial care. Such patients can be helped to rehabilitate themselves to their maximum potential. They should be adequately treated, and to accomplish this, we should broaden our own horizons.

The definition of adequate therapy has varied over the past ten years. From the original 42-day courses of streptomycin, treatment was first extended to a period of six months, then to one year, and today most of my patients are treated for at least two years. In fact, recent reports have suggested that many patients require indefinite treatment—possibly for the rest of their lives—in order to maintain a negative sputum and to prevent a relapse or re-activation. Our present drugs are bacteriostatic and not bacteriocidal, so that the tubercle bacillus is not actually destroyed by them. Many patients with old fibro-cavernous disease will not be cured, but can be maintained in their own homes, in a non-contagious condition and able to live a moderately normal life.

At present, the most effective chemotherapeutic agents are streptomycin, dihydrostreptomycin, PAS, and isoniazid. When used over long periods of time, the ototoxic effects of the streptomycin drugs are well known. It is also established that in the older patient auditory acuity normally decreases, probably due to otosclerosis. Thus it is important to do everything possible to diminish any auditory toxicity of the streptomycin drugs.

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STUDIES OF NEUROTOXICITY OF STREPTOMYCIN DRUGS

Both laboratory (2, 3, 4) and clinical studies (5, 6) have demonstrated that streptomycin causes, predominantly, vestibular dysfunction and dihydrostreptomycin, auditory impairment. To avoid or minimize these ototoxic effects, a mixture of equal parts (0.5 Gm. each) of streptomycin and dihydrostreptomycin, known as streptoduocin, was suggested (Dr. L. B. Hobson). As it was known that the toxic effect of each drug could be greatly reduced when given in 0.5-Gm. dosage, it was thought that the combination would be therapeutically effective. Studies with laboratory animals receiving streptoduocin indicated that it was less toxic than streptomycin with regard to the vestibular apparatus (2, 3). California investigators (7–9), the Sita-Lumsden group (10), and our own workers (11–13) have since demonstrated clinically that streptoduocin is less toxic than equivalent doses of either streptomycin or dihydrostreptomycin for the auditory and vestibular functions (14).

The present study concerns the neurotoxicity of streptoduocin, with PAS (para-amino salicylic acid) or INH (isonicotinic acid hydrazide, or isoniazid), when administered twice weekly for eighteen months, compared with that in controls receiving either streptomycin or dihydrostreptomycin for a similar period of time. This is a continuation of our studies covering four, eight and twelve months of treatment.

As previously reported (11–13), after four months of daily or semi-weekly streptoduocin therapy, there were neither auditory nor vestibular ototoxic effects in 272 patients. In 136 controls receiving daily doses of streptomycin or dihydrostreptomycin there was a 30 per cent incidence of vestibular damage with streptomycin and 26 per cent incidence of impaired hearing with dihydrostreptomycin, whereas in 136 controls receiving semi-weekly treatment there was a 5 per cent incidence of vestibular damage with streptomycin, and 4 per cent incidence of cochlear injury with dihydrostreptomycin.

After twelve months of semi-weekly injections of streptoduocin in a group of 210 patients, 4 showed evidence of vestibular damage and 2 showed cochlear injury, *i.e.*, a 2 per cent incidence of vestibular, and 1 per cent incidence of cochlear impairment, respectively. A control group of 130 patients receiving semi-weekly injections of streptomycin for twelve months showed an incidence of 7 per cent vestibular disturbance and 1 per cent cochlear injury. A similar group of 94 patients, receiving dihydrostreptomycin twice weekly for twelve months had a 2 per cent incidence of vestibular damage and 8 per cent cochlear impairment. Thus, although the clinical response, as measured by such criteria as cavity size or sputum conversion, was very similar under all three regimens, the toxic effects were definitely reduced in patients receiving streptoduocin.

For the eighteen-month study, streptoduocin was administered to 151 patients with moderately advanced or far advanced pulmonary tuberculosis (including about 6 per cent extrapulmonary, either renal or gastro-intestinal). Control groups consisted of 62 patients who received streptomycin and 24 patients who received dihydrostreptomycin. The streptomycin drugs were given

TABLE 1

	Vestibular Damage (%)		Cochlear Damage (%)	
	Daily therapy	Semi-weekly therapy	Daily therapy	Semi-weekly therapy
Four Months				
Streptomycin (136 patients)	30	5	6	0.5
Dihydrostreptomycin (136 patients)	5	1	26	4
Streptoduocin (272 patients)	0	0	0	0
Eight Months				
Streptomycin (136 patients)		6		0.5
Dihydrostreptomycin (136 patients)		1		6
Streptoduocin (272 patients)		1		0
Twelve Months				
Streptomycin (130 patients)		7		1
Dihydrostreptomycin (94 patients)		2		8
Streptoduocin (210 patients)		2		1
Eighteen Months				
Streptomycin (62 patients)		10		2
Dihydrostreptomycin (94 patients) 24		4		12.5
Streptoduocin (151 patients)		2.7		1

in 1-Gm. injections twice weekly, with the usual dosage of INH (200–300 mg. daily) or PAS (12–16 Gm. daily). Due to transfer from our hospitals, or death, the original streptoduocin study group of 272 patients was reduced to 151 patients, and the control group were similarly reduced (Table 1).

In the streptoduocin-treated group of 151 patients, 4 showed vestibular damage and 2 had evidence of cochlear injury, *i.e.*, 2.7 per cent incidence of vestibular and 1.3 per cent incidence of cochlear impairment. There were very few allergic reactions, and none necessitated omission of treatment. In the 62 control streptomycin patients, after eighteen months of semi-weekly treatment, the incidence of vestibular damage was 10 per cent and of cochlear injury, 1.6 per cent. In a similar group of 24 patients who received semi-weekly dihydrostreptomycin for eighteen months, the corresponding incidences were 4 per cent and 12.5 per cent (Table 1).

SUMMARY AND CONCLUSIONS

The streptomycin group of drugs in combination with INH and/or PAS is the therapy of choice for most patients suffering with tuberculosis. As these are bacteriostatic and not bacteriocidal agents, the period of treatment has been prolonged. At present, moderately or far-advanced tuberculosis is treated with these drugs for two years or longer, instead of for only forty-two days as in the early days of streptomycin therapy. In view of the longer period of treatment and the more advanced age of the patients, the toxic effects on the vestibular and cochlear organs assume greater significance.

In our series, patients receiving streptoduocin (0.5 Gm. each of streptomycin and dihydrostreptomycin) twice weekly showed no toxic effects after four months.

After twelve months, the incidence of toxic effects on the vestibular apparatus was about one fourth as great with streptoduocin as with streptomycin; on auditory function, it was one eighth as great as with dihydrostreptomycin.

During administration of streptoduocin twice weekly for eighteen months, toxic effects on the labyrinthian apparatus occurred one fourth as frequently as with streptomycin; and on the cochlear apparatus, one twelfth as frequently as with dihydrostreptomycin.

As a result of these studies, it is our belief that streptoduocin has the therapeutic effects of each of its components, but with a marked decrease in their toxic effects. Streptoduocin, administered with the usual supplemental drugs, is therefore preferred to either streptomycin or dihydrostreptomycin.

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OSTEOPOROSIS—A GERIATRIC PROBLEM

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Osteoporosis occurs most frequently after the age of 50 and is, therefore, primarily a geriatric problem. The subjective response to medical and orthopedic treatment is good. The condition is principally a protein metabolic disorder, and is only secondarily concerned with calcium, phosphorus and alkaline phosphatase activity. After the age of 50 normal osteoblastic function may be less active because of hormonal changes, particularly in women following the menopause, so that some degree of osteoporosis may be considered physiologic. Studies by Reifenstein and Albright (1) (quoted by Hollander (2)) showed that bone production is at a minimum in osteoporosis. Inadequate bone formation is the result of an insufficient production of matrix due to a lack of "protein-building blocks" and only secondarily to diminished deposition of calcium.

ETIOLOGY

Three prime factors influence osteoblastic activity: steroids, mechanical stresses and strains, and nitrogen-building blocks. Albright and Reifenstein (3) (quoted by Harrison (4)) believe these are the main elements involved in osteoporosis. There is the possibility of an unknown fourth factor.

1. Steroids: It is known that the pituitary, adrenals and gonads are concerned with catabolic activity. Estrogen and androgen are anabolic, adrenocortical "S" (sugar) hormone is anti-anabolic, and progesterone is anabolically inert. Adrenocorticotropic hormone (ACTH), with its secondary action on the adrenal cortex, has a catabolic action. When there is a balance between "breaking down" and "building up," such "negative-nitrogen" conditions as osteoporosis do not occur. Only when there is imbalance between anabolism and catabolism may metabolic disturbances, such as osteoporosis, result.

2. Mechanical stresses and strains: Those associated with weight bearing and use, are important stimuli for normal osteoblastic activity (bone deposition). However, in osteoporosis, stress may result in bony injury.

3. Nitrogen-building blocks: Protein deficiency may be due to an inadequate intake of proteins (especially the essential amino acids), poor assimilation, or excessive breakdown of the structural material, resulting in a negative nitrogen balance.

4. Since all factors in osteoporosis are not yet fully understood, a fourth factor, "X," may be added to those suggested by Albright.

Serum calcium, phosphorus and alkaline phosphatase levels are usually normal in osteoporosis. Microscopically, bone sections show few osteoclasts, and osteoblasts are rare.

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TYPES OF OSTEOPOROSIS

There are certain clinical symptoms and signs which indicate that the possibility of osteoporosis should be investigated. If an asthenic patient of about 60 years of age appears older, complains of back pains, has a rounded hollow back or has hip discomfort, and the findings on clinical examination of the joint are negative, a provisional diagnosis of osteoporosis is tenable. Numerous varieties of osteoporosis have been described, but the more common types are seen in older patients and will be briefly discussed.

Postmenopausal osteoporosis is considered by Albright *et al.* (3) to be the most common of the systemic osteopathies. Reifenstein *et al.* (1), on roentgen study, observed deossification in 50 per cent of women beyond the age of 50 (postmenopausal), although symptoms were present only in about 10 per cent of this group. At this age there is a decline in the production of estrogen, which may induce a decrease in protein metabolism and result in decreased osteoblastic activity with inadequate bone formation. Estrogen deficiency, regardless of cause, may result in osteoporosis. Other important factors are the compensatory production of other anabolic substances, the amount of calcium and phosphorus in the skeleton at the time of onset, diet, and the activity of the patient.

Senile osteoporosis is similar, in most aspects, to the postmenopausal type seen in women. The term "senile osteoporosis" has been used when the disturbance becomes manifest after the age of 65 (4). Gershon-Cohen and one of us (A.M.R.), in examining 136 relatively healthy individuals in the Home for the Jewish Aged in Philadelphia, found that x-ray and clinical studies revealed senile osteoporosis (5) in 25 per cent. Insufficient food intake, lack of protein foods, disuse and hormonal deficiency are important factors in this type of osteoporosis. Many older people delete certain foods from their diet because of the mistaken idea that these foods are harmful. Meat is a food most frequently omitted. The total caloric intake may be low and a negative nitrogen balance may ensue, resulting in loss of bony matrix and other protein tissues. The defect is due to failure of the osteoblasts to deposit bone in the trabeculae.

Disuse osteoporosis: In young individuals this is usually a local disturbance, frequently associated with disuse resulting from immobilization of an injured part.

Generalized osteoporosis often occurs in older people, who are bedridden because of such conditions as cerebral vascular accidents, fractured hips, generalized weakness, cardiac and psychiatric disorders.

Other diseases and drugs may induce osteoporosis. Cushing's syndrome and acromegaly may be associated with osteoporosis, as may hyperthyroidism and avitaminosis. Osteoporosis following administration of ACTH is an example of the drug-induced type.

SIGNS AND SYMPTOMS

On x-ray study, osteoporosis is frequently seen in the spine, pelvis and femur, but it must be remembered that deossification alone is not sufficient to establish a diagnosis of osteoporosis. Although degenerative hypertrophic fringing, spur-

ring and osteophytes, particularly of the spine, are commonly observed on roentgen study in older individuals, it has been our observation (6) that these findings are either absent or minimal in patients of similar age who have osteoporosis. The deossified bone is shown as a lighter shadow, so that, paradoxically, the cortical outline appears to be more distinct and the bone is opalescent. The trabeculae are thin and the spaces between are larger than usual. The process is one of deossification, not decalcification. However, when there is a fracture, union tends to occur, though more slowly than in the normal subject, and the roentgenogram shows increased bone density at the healing fracture site. In the spine, the disc spaces are usually bi-convex because the disc, with its nucleus pulposus, expands to compress the adjacent surfaces of the deossified vertebral bodies. These, in turn, appear biconcave—the so-called "codtail vertebrae." Compression fractures of the vertebral bodies may occur and may resemble the usual type of traumatic wedging. More frequently, however, the body may be compressed and buckling of the anterior cortex is seen.

Hip discomfort in older individuals should suggest the need for excluding a fatigue fracture. Although the clinical examination of the hip may result in negative findings, the x-ray study may show a partial, linear, incomplete or fatigue fracture in the neck of the femur. Adequate attention at this time may prevent complete solution of the continuity of the bone with its potential hazards. Backache in older people suggests the need for study to ascertain if the patient has senile osteoporosis with a compression fracture. Such fractures invariably are precipitated by a relatively minor incident or injury, such as stepping from a curb which is a bit higher, or sitting on a chair that is a bit lower than anticipated.

DIFFERENTIAL DIAGNOSIS

Other clinical and radiologic conditions should be considered in differential diagnosis of lesions associated with deossification. Hyperparathyroidism is due primarily to a disturbance of the parathyroid glands. The serum calcium and alkaline phosphatase levels are elevated and that of phosphorus is decreased. Renal stones may be a secondary complication. There is generalized bone involvement in the skull, spine, pelvis and long bones, with cystic changes and egg-shell thinning of the cortex; pathologic fractures and deformities are usual.

Generalized Paget's disease (osteitis deformans) is associated with extremely high serum alkaline phosphatase levels. The skull, vertebrae, pelvis and long bones are often involved. In the latter, the cortex is widened and the medullary canal is narrowed. The disturbance is usually biphasic.

Osteomalacia (adult rickets) is the result of failure of calcium deposition in osteoid tissue. Renal acidosis and the steatorrheas may cause similar changes. The serum calcium and alkaline phosphatase levels are changed, depending on compensatory parathyroid activity. Osteomalacia is associated with bone demineralization, whereas osteoporosis in its many manifestations is associated with deossificaton.

Bone pain may be the first symptom of multiple myeloma, or of compression fracture of the vertebral bodies. The process is usually more localized than in osteoporosis. There is often albuminuria, an increase in the levels of serum globu-

lin and total protein, and a reversal of the A/G ratio. The presence of plasma cells in the bone marrow and peripheral blood, and the detection of Bence-Jones protein in the urine, establish the diagnosis. Vitamin C deficiency depresses osteogenesis. Osteogenetic sarcoma, metastatic malignancy and leukemia should be considered in the differential diagnosis of all cases of deossification.

PROGNOSIS AND TREATMENT

Although prognosis may vary with the etiologic factor, in general it may be considered guardedly favorable for relief of symptoms and rehabilitation of the patient. Subjective relief is often apparent within a few weeks, even though x-ray studies may not show reossification of the bones.

Treatment is preventive, medical and orthopedic. When the cause is known, the remedy may be evident. If a local part must be immobilized, especially in an older patient, general activity should be encouraged to a degree which is practical. If it is necessary to confine an older patient to bed, deep breathing, frequent turning and local exercises (active or, if need be, active-assisted) are important. The urine and genito-urinary tract should be examined for infection and calculi, and concentration of the urine should be prevented by a high fluid intake, particularly in the presence of calcinuria. Narcotics are rarely indicated, as they favor inactivity and disuse of the affected parts, thus setting up a vicious cycle. The pain usually responds to steroid-type hormones, salicylates and vitamins used in conjunction with the other measures. In older people it is necessary to assure an adequate protein intake and encourage general activity, particularly of previously immobilized parts. Proper fluid intake and weight regulation are important in the prevention of osteoporosis. In caring for the aged, the doctor should be on the alert to prevent or detect malnutrition. The use of supplemental vitamin D, or other vitamins and minerals is rarely necessary if food intake is adequate. Their unwarranted use may result in the formation of renal calculi. Hormones, such as estrogen and androgen are paramount in the medical treatment of osteoporosis. In our practice we use Premarin® (1.25 mg.) and methyltestosterone (10 mg.); these are given orally twice daily for one week, then once a day for three weeks, with a rest period of one week before a second course is begun, if the symptoms warrant. After the foregoing medication has been given for about two weeks, or when the subjective annoyance is improved, the dose may be halved for maintenance therapy. Because estrogen may stimulate the breast and uterus, the patient should be told that bleeding (withdrawal type) may occur during the free period. The combination of drugs mentioned is available in a single tablet. In addition, we often give injectable testosterone in 25-mg. doses three times a week. Recently Goldzieher and Goldzieher (7) suggested the use of testosterone cyclopentylpropionate, a depo® preparation, which they feel has a longer duration of action and a greater anabolic effect. They used 50 to 100 mg. per week, in addition to estrogen therapy. Of the two chief drugs used in the treatment of osteoporosis, estrogen affects calcium retention, whereas androgen mainly affects nitrogen retention. Since these hormones complement each other in the retention of calcium, they should be used together.

Orthopedic procedures are very important in the treatment of osteoporosis.

In general, this consists of measures to relieve strain, spasm and pain. Additional benefit is derived from the use of a non-resilient bed, obtained by placing a plywood board between the spring and mattress, by tying down the bed springs, or by using a horsehair mattress without springs. When prescribing mechanical support, the patient's age, type and temperament should be considered. Aged people often cannot or will not wear corsets or braces. A front-laced, well boned corset with a closed back usually furnishes ample support to patients with vertebral fractures. A Knight spinal brace, when tolerated, is excellent. A Taylor spinal brace or plaster jacket is usually not tolerated by older people and often provides more support than is required. It is better to compromise a little and have a support that the patient will wear rather than a very efficient garment which the patient will not, or cannot endure. In fractures of the neck of the femur, early pinning and mobilization are important in order to prevent disuse osteoporosis. Fractures in patients with osteoporosis may heal slowly, but generally there is good bony union.

SUMMARY AND CONCLUSIONS

Osteoporosis is common in older people. It is primarily a disorder of protein metabolism. Treatment usually relieves the subjective complaints, even though the x-ray changes resulting from reossification may not be evident for years. Aged people should be instructed in maintaining an adequate and balanced diet, high in protein, and told to report for clinical and radiologic examination as soon as there is discomfort in the region of the hip or back. The physician likewise should be on the alert for complications of osteoporosis, particularly fatigue fractures. Medical and orthopedic measures should be started early and the patient should be kept under observation for a long period.

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TREATMENT OF FRACTURES OF THE NECK OF THE FEMUR IN THE AGED*

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The introduction of the three-flanged nail by Smith-Petersen in 1931 (1) changed the entire concept of the management of patients with fracture of the neck of the femur. Recent appraisal (2–4) of end-results indicates the problem is far from solved. The mortality has been lowered. This method has obviated the use of plaster and prolonged immobilization of the patient with the resulting disabilities and complications, such as hypostatic pneumonia and pressure sores. The operation results in immediate relief of pain and eases nursing care. The patient is permitted freedom of all activity except actual weight bearing.

The unsolved aspects of the problem relate to the nature of the femoral-neck fracture itself. Non-union, aseptic necrosis and degenerative arthritis still complicate the picture. In spite of adequate reduction and fixation, aseptic necrosis of the femoral head may result because of interruption of the blood supply; the incidence may reach a high level especially if the patients are followed for two or more years. Aseptic necrosis may occur in conjunction with non-union; however, non-union can develop in the presence of a viable femoral head as a result of inadequate reduction and fixation. Loss of position at the fracture site also occurs, occasionally, because of poor nailing and often because the degree of contact at the fracture line is faulty. In some patients degenerative arthritis develops as a result of the fracture.

CLINICAL MATERIAL AND METHODS

All of these factors led us to an assessment of our results in an effort to determine the functional capacity of our patients and the measures necessary for improvement of results. This review covers the patients with fracture of the neck of the femur admitted to the State University of Iowa hospitals from 1940 to 1952, inclusive. The majority of these patients were treated by the resident staff; some were treated by the senior staff. It has been our policy to classify these fractures as surgical emergencies. Internal fixation is usually performed within twenty-four hours following admission, after adequate hydration and restoration of blood volume. Postponement of operation is necessary in patients who present marked hypovolemia and systemic diseases which necessitate further preoperative preparation, *e.g.*, diabetes mellitus, congestive heart failure, or uremia.

The patient is placed on a fracture table, and each extremity is fastened to a foot piece. Reduction in most instances is accomplished by traction, internal rotation and abduction of the injured extremity. When adequate reduction is not ac-

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complished by this method, the involved extremity is released from the foot piece and a Leadbetter (5) maneuver performed. It has been our experience that it is inadvisable to attempt the Leadbetter procedure as an initial maneuver. In some instances it causes extreme rotation of the femoral head, making an otherwise unnecessary open reduction mandatory. Roentgenograms in both anteroposterior and lateral planes are necessary in order to determine the status of the reduction and to guide accurate insertion of the Smith-Petersen nail.

The usual hospital stay of these patients is approximately ten days. On discharge, they are instructed to avoid all weight bearing, even on the uninjured extremity. (Unfortunately, they do not always follow this admonition.) The fracture is checked by roentgenograms at intervals of three months over a period of one year. At the end of six months, if healed, gradual weight bearing with crutches is permitted. Some patients with a stable fracture may be allowed non-weight-bearing crutch walking at three months. (Ideally, a roentgenographic check every six weeks for the first six months is desirable; thereafter, every three months for at least two years.)

STATISTICS

During the period 1940–1952, inclusive, 199 patients 60 years of age and older were admitted to the University Hospitals for treatment of fracture of the femoral neck. Of these, 25 were in the age group 60–64, and 174 were 65 years of age and older. Among the latter, 34 patients were in the 65–69 group, 38 were in the 70–74 group, 41 were in the 75–79 group and 61 were 80 years of age and over (Table 1). Eleven patients died preoperatively. Twenty-three patients died during operation or in the immediate postoperative period—a mortality rate of 12.2 per cent. The mortality by age groups is tabulated in Table 2. It is to be noted that approximately 50 per cent of the deaths occurred in the age group of 80 or over. The 31 patients who died within one year following discharge were not

TABLE 1. *Age Distribution of Patients with Fractures of the Femoral Neck*

Age (yrs.)	No. of patients
60–64	25
65–69	34
70–74	38
75–79	41
80 and over	61
Total	199

TABLE 2. *Mortality by Age Groups*

Age group	Preop. deaths	Operative and postop. deaths
60–64	1	0
65–69	0	1
70–74	3	4
75–79	4	3
80 and over	3	15
Totals	11	23 (12.2%)

TABLE 3. *Follow-up Data*

1. Died within first year after surgery	31	
2. Alive for follow-up	134	
3. Follow-up letters not answered	43	
4. Follow-up letters answered	91	
5. Walked without cane or crutch; no visible deformity	41	(45.0%)
6. Walked without cane or crutch, but with visible deformity	10	(10.9%)
7. Walked with cane or crutch	16	(17.5%)
8. Walked with cane or crutch but had arthritis	2	(2.1%)
9. Did not walk after operation, but were invalids prior to fracture	7	(7.6%)
10. Total permanent invalids	15	(16.4%)
11. Total walking at time of follow-up	69	(75.8%)

TABLE 4. *Non-Union by Age Groups*

Age group	Number
60–64	2
65–69	4
70–74	4
75–79	3
80 and over	6
Total	19

considered in this analysis, because it is felt they died too early for proper evaluation of the fracture. The tabulation of follow-up data is presented in Table 3. Letters of inquiry were sent to all who were discharged and to their family physicians. We were unable to trace 43 patients adequately. Follow-up reports were received on 91 patients.

Forty-one patients (45.0 per cent) were walking without cane or crutch and without visible deformity. Ten patients (10.9 per cent) were walking without cane or crutch but with evidence of visible deformity. Sixteen patients (17.4 per cent) were walking with cane or crutch. Two patients (2.1 per cent) were walking with cane or crutch but were known to have had arthritis before the fracture was incurred. Seven patients (7.6 per cent) were bedfast invalids before the fracture occurred and never walked after operation. Patients were classified as permanent invalids who did not walk again following the internal fixation. There were 15 such patients (16.4 per cent). (This figure does not include the 7 patients who were bedfast prior to the fracture.) The total number of patients who walked was 69 (75.8 per cent).[1]

In reviewing the roentgenograms, 19 showed non-union of the fracture. Of these, 4 showed an adequate reduction and 15 did not. Table 4 lists these cases by age groups. The results in these 19 patients whose fractures showed non-union were as follows: 7 walked with cane or crutch; 5 walked with a visible deformity; and 7 never walked after operation.

Some patients showed both non-union and aseptic necrosis. These are included

[1] Nineteen of the patients from whom no follow-up letters were received were walking at the time they were seen on their last check-up examination, or the roentgenograms showed evidence of union. If we include this group of patients, 98 out of the total of 110 (80.0 per cent) walked.

TABLE 5. *Aseptic Necrosis (with and without non-union) by Age Groups*

Age group	Number
60–64	5
65–69	7
70–74	0
75–79	2
80 and over	7
Total	21

in the foregoing results and in Table 4. Nine patients had union of the fracture but with aseptic necrosis. Age played no significant role in the incidence of aseptic necrosis. Table 5 lists all the patients with aseptic necrosis by age groups, including those with non-union, tabulated in Table 4. The results in the patients with aseptic necrosis were as follows: 5 walked without difficulty; 6 walked with cane or crutch; 2 walked with visible deformity; and 8 never walked after operation.

DISCUSSION

These results are surprising, in that a significant number of patients who were designated as probable permanent invalids because of the roentgen appearance of non-union and/or aseptic necrosis have become ambulatory. Their functional capacity is not as poor as one might have predicted on the basis of the roentgenograms. However, to improve these results it is necessary to impose more rigid criteria: 1) with respect to reduction and nailing, and 2) with respect to early recognition of loss of position, impending non-union and aseptic necrosis.

If an anatomic reduction is not possible, the preferred reduction is one in which the femoral head is directed toward valgus position and the inner medial portion of the neck fragment lies inside the medial portion of the head fragment. This is the picture seen in a so-called "abduction type" fracture (Fig. 1). This type usually leads to a higher percentage of bony union. The muscle pull and thrust of weight tend to impact the head and neck without creating a shearing force. A fracture in which reduction is inadequate displays a neck which is pushed outward and up, bypassing the head; the shearing force is therefore transferred to the fixation nail, which cannot maintain its hold in the bone (Fig 2). In these instances, open reduction accompanied by internal fixation may be necessary. It appears from the results that primary bone grafting may be advisable in the following: fractures which appear unstable because of persistence of an oblique fracture line after reduction; unstable comminuted fractures; subcapital fractures in which an open reduction is carried out and an inadequate blood supply is apparent at the time of operation; untreated fractures three or more weeks old. Bone grafting is performed by insertion of a tibial bone graft supported by two or three threaded Steinman pins (Fig. 3).

In those fractures of the femoral neck which cannot be satisfactorily reduced without the aid of open reduction, it has been advocated (6) that an immediate

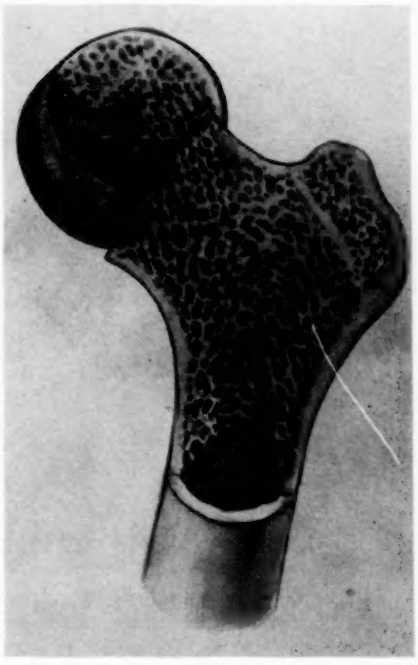

FIG. 1. "Abduction type" fracture

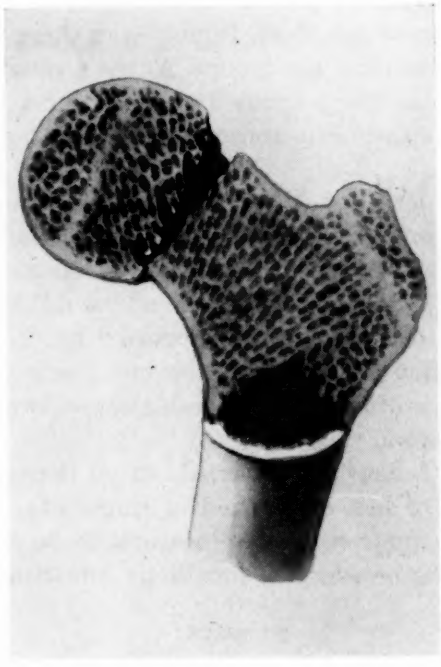

FIG. 2. Inadequate reduction

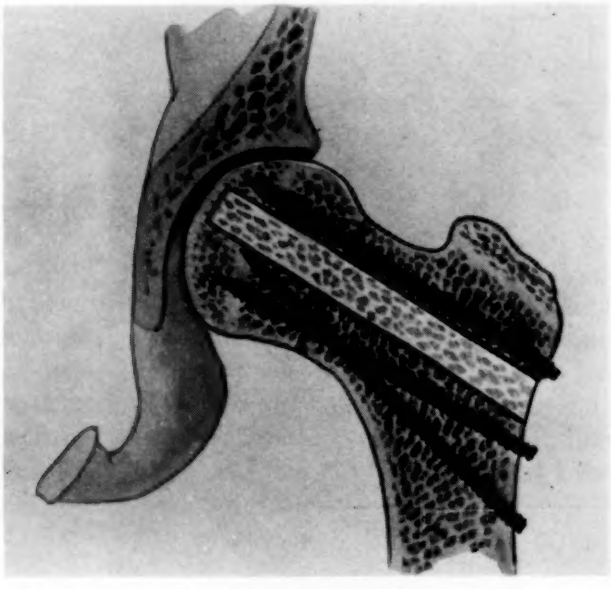

Fig. 3. Bone graft, with threaded Steinman pin fixation

osteotomy be performed in order to change the fracture line to a more horizontal plane. In these instances, we prefer to perform an open reduction, supported by the bone grafting procedure.

It has been suggested that a prosthesis be used instead of nailing, especially in patients over 75 years of age (7–9). In our series there was no indication that union fails to occur in the older age groups. At the present time we do not feel a prosthesis is advisable as the primary treatment for a fractured neck of the femur. No prosthetic replacement approaches the value of a united fracture of the neck of the femur.

When there is non-union after an acceptable reduction we advocate removal of the Smith-Petersen nail and insertion of a tibial bone graft in the freshened nail tract, with fixation of the fragments by means of threaded Steinman pins. In early aseptic necrosis of the femoral head we advise drilling of the femoral head and insertion of two tibial bone grafts supported by threaded Steinman pins. When definite destruction of the head is beyond repair or when absorption of the neck precludes restitution by a favorable union, we advise prosthetic replacement of the Thompson type (10).

It is important that follow-up be carried out on these patients after nailing. The early recognition of loss of position of fragments, non-union, or aseptic necrosis will enable adequate corrective measures to be employed in promoting union, thus avoiding the necessity of prosthetic substitution.

SUMMARY

1. Results following fixation of fractures of the neck of the femur by a Smith-Petersen nail have been reviewed. A surprising number of patients are able to walk with evident non-union or aseptic necrosis, or both.

2. Satisfactory results are dependent upon adequate reduction. If necessary, open reduction should be instituted. At times this is supplemented by a bone graft with threaded Steinman pin fixation.

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Abstracts of Current Literature

AORTIC STENOSIS—CLINICAL MANIFESTATIONS AND COURSE OF THE DISEASE. REVIEW OF ONE HUNDRED PROVED CASES.

Bergeron, J.; Abelmann, W. H.; Vasquez-Milan, H., and Ellis, L. B. *A.M.A. Arch. Int. Med.* **94:** 911 (Dec.) 1954.

The clinical and necropsy records of 100 patients with aortic stenosis were studied in order to determine to what extent the degree of aortic stenosis and the course of the disease could be predicted from signs and symptoms. Aortic stenosis was marked in 49, moderate in 32, and mild in 19 cases. The mean age was 69 years and the ratio of males to females 3:1. Pain referable to the heart occurred in one-third, dizziness in one-quarter, and syncope in one-eighth of the patients. Pain was diagnostic of angina pectoris in only half of those in whom it occurred. Typical angina was more often accompanied by coronary atherosclerosis than was atypical cardiac pain. When severe aortic stenosis was present, the systolic basal thrill and murmur might be absent, the second aortic sound judged normal, and the diastolic pressure low and associated with a wide pulse pressure. A harsh systolic murmur, loudest at the apex or heard only there, was sometimes the only physical sign. Systolic and/or diastolic hypertension was present in 33 per cent of the patients, and there was electrocardiographic evidence of left ventricular hypertrophy in 38 per cent of the tracings reviewed, and auricular fibrillation in 30 per cent. The nature and severity of the symptoms, and the blood and pulse pressures aided little in determining the degree of stenosis, perhaps because of the degree of associated coronary atherosclerosis, myocardial fibrosis and aortic regurgitation. The rapid evolution of symptoms, the absence of a second aortic sound, and the presence of an aortic systolic murmur Grade IV or louder, or an aortic systolic thrill favored marked stenosis. A narrow pulse pressure indicated moderate to marked stenosis. The asymptomatic phase of the disease was often long and permitted the attainment of advanced age, but when cardiac symptoms appeared the prognosis became guarded. Congestive failure and auricular fibrillation were grave signs. Death followed in weeks or months when cardiac pain or syncope accompanied either.

CEREBRAL VASCULAR DISORDERS.

Brain. R. *Ann. Int. Med.* **41:** 675 (Oct.) 1954.

Two series of patients with cerebral vascular disease are analyzed with special reference to correlation between age distribution and type of lesion. Whereas 67 per cent of the 100 private patients were over the age of 60, only 37 per cent of the 100 hospital patients were over this age. The two series differ in this respect because acute cerebral vascular lesions requiring hospitalization occurred most frequently in the younger age groups. Subarachnoid hemorrhage, angioma, and aneurysm were all most frequent in patients under 60 years of age. Degenerative diseases were most frequent in the 60 to 70 year old group. The disorders present in the 200 patients (some had more than one), in percentages, were as follows: intracranial aneurysm, 8; intracranial angioma, 8; subarachoid hemorrhage, 15; cerebral embolism, 1.5; migraine, with permanent hemianopsia, 2.5; cerebral arteriosclerosis, 38.5; cerebral infarction, 23.5; cerebral hemorrhage, 3; benign hypertension, 48; and malignant hypertension, 1.5. The principal symptoms and numbers of patients with each were as follows: subarachnoid hemorrhage, 30; hemiplegia or monoplegia, 28; epilepsy, 18; dementia, 9; parkinsonism, 8; aphasia, 6; hemianopsia, 6; pseudobulbar palsy, 3; involuntary movements, 3; thalamic hemiplegia, 2; and minor episodes, 87.

THE RATIONALE FOR RADICAL PANHYSTERECTOMY AND PELVIC NODE EXCISION IN CARCINOMA OF THE CORPUS UTERI. CLINICAL AND PATHOLOGICAL DATA ON THE MODE OF SPREAD OF ENDOMETRIAL CARCINOMA.

Brunschwig, A., and Murphy, A. I. *Am. J. Obst. & Gynec.* **68:** 1482 (Dec.) 1954.

Because of the widely held belief that metastases from corpus cancer are so extensive that local treatment in the pelvis affords no control, the desirability of pelvic lymph node excision in the surgical treatment of corpus cancer has largely been overlooked. Pathological findings in 17 patients with advanced disease in whom some type of exenteration was performed indicate that endometrial carcinoma spreads in a manner similar to that of epidermoid carcinoma of the cervix, first involving the adjacent viscera. Pelvic lymph node metastases were observed in 4 patients. Modern surgical management of malignant neoplasms in the abdomen involves wide resection of lymph nodes likely to be the first site of metastases. Therefore, the treatment of corpus cancer should include pelvis lymph node excision as well as radical panhysterectomy, whenever possible. Simple total hysterectomy for endometrial carcinoma does not represent the maximal surgical effort. Patients with corpus carcinoma are generally older and are poorer operative risks than those with cancer of the cervix. In a series of 57 carefully selected patients who underwent radical panhysterectomy and concomitant pelvic lymph node excision for corpus carcinoma, the surgical mortality was zero. Ten patients were found to have pelvic lymph node metastases. The series is too small for the postoperative results to be of significance in evaluation of the operation.

THE EFFECT OF CONGESTIVE HEART FAILURE ON BLOOD VOLUME AS DETERMINED BY RADIOCHROMIUM-TAGGED RED CELLS.

Eisenberg, S. *Circulation* **10:** 902 (Dec.) 1954.

Total blood volume, red cell mass, and plasma volume have been determined with radiochromium-labeled red cells in 26 patients with congestive heart failure. The patients were categorized as *mild*, *moderate* or *severe* according to the duration, severity and tractability of the congestive process. Measurements of blood volume, red cell mass and plasma volume in subjects with congestive heart failure exceeded the values for a group of normal subjects by 22 per cent, 25 per cent and 17 per cent. In patients with *severe* congestive heart failure the measurements of blood volume exceeded those of the normal group by 38 per cent; in the *mild* group the values exceeded those of the normal group by only 14 per cent. The magnitude of the hypervolemia was correlated with the degree of cardiac enlargement but not with the increase in venous pressure, etiology of the heart disease, or quantity of edema fluid. The circulating red cell mass was consistently expanded during the congestive state; selective expansion of the plasma volume was not observed. Following treatment, the blood volume decreased significantly in 50 per cent of the cases; shrinkage in blood volume occurred only in those subjects in whom the heart size decreased with treatment. The quantity of edema fluid was not correlated with the expansion of plasma volume prior to treatment or the decrease in plasma volume following treatment. (From author's conclusions.)

PRECURSORS OF CORPUS CANCER. II. A CLINICAL AND PATHOLOGICAL STUDY OF ADENOMATOUS HYPERPLASIA.

Gusberg, S. B.; Moore, D. B., and Martin, F. *Am. J. Obst & Gynec.* **68:** 1472 (Dec.) 1954.

The histology, clinical pattern, and possible cancer significance of 100 cases of adenomatous hyperplasia of the endometrium are discussed. For some time, this atypical hyperplasia has been considered a possible cancer precursor. In this study, 64 of the 100 patients reported having menorrhagia, metrorrhagia, or both. Of 33 postmenopausal patients, 29 had postmenopausal bleeding. Twenty-two of the 100 patients had received estrogenic preparations before the onset of vaginal bleeding. Twenty-four of the 37 patients, treated

by curettage only, were considered cured; 13 required further treatment. Of the 26 patients who were treated with curettage followed by radiation sterilization, 23 were considered cured, and 3 required further treatment. Thirty-six patients were treated by hysterectomy. Cancer was found coexistent with adenomatous hyperplasia of the endometrium in 8 patients. It developed later in 2 patients. In 10 patients, coexistent lesions of borderline malignancy were found. Since 36 patients were treated by hysterectomy, and of the remaining 64 patients only 23 were followed for over six months, a complete evaluation of the relationship of adenomatous hyperplasia to endometrial cancer was not possible. However, the number of cases of cancer and possible cancer found indicates that adenomatous hyperplasia is a cancer precursor in this area and should be so regarded when planning treatment.

PRIMARY CARCINOMA OF THE MALE URETHRA.

Hotchkiss, R. S., and Amelar, R. D. *J. Urol.* **72:** 1181 (Dec.) 1954.

Carcinoma of the male urethra, although uncommon, is not a rarity. Six cases discovered among 10,080 urologic admissions during a ten-year period at Bellevue Hospital are summarized and literature on the subject briefly reviewed. Chronic irritation appears to be a significant etiologic factor, 48 per cent of patients having had a coexistent stricture. The typical sequence of events is gonococcal urethritis, stricture and difficulty with urination, peri-urethral abscess, drainage, and fistula formation; biopsy is then performed as the only means of establishing the diagnosis. The cases presented illustrate the wide variety of cellular structure of these tumors. Metastases were reported in 15 per cent of cases. The superficial and deep inguinal nodes are the first lymphatic nodes to be involved. Distant metastases occur more commonly when the carcinoma is in the posterior portion of the urethra. Effective control cannot be anticipated unless the lesion is diagnosed at an early stage of its development, but this is infrequently accomplished. Treatment is essentially surgical. External radiation is customarily restricted to adjunctive therapy and, in general, has been ineffective. Amputation of the penis with dissection and removal of the pre-symphyseal and inguinal nodes is indicated when the carcinoma is located in distal portions of the urethra. Carcinoma in the proximal portion implicates the pelvic nodes and they must be extirpated when adenectomy is performed for removal of a tumor in this portion of the urethra.

MODERN VIEWS ON HEALTH PROBLEMS OF AGING.

Ingraham, H. S. *Connecticut M. J.* **43:** 963 (Dec.) 1954.

Health problems of the rapidly increasing older portion of the population are discussed with reference to population changes, mortality rates, and health department programs in New York State. Today's health problems concern the sickness and disabilities of middle and old age. Communicative disease control, formerly an urgent problem, now chiefly entails continuance of preventive measures. Modern views on the health problems of the aged take into account the growing realization that old people can make an important contribution to modern life and that society needs their productive capacity. Old age is not in itself a disease, and many of the disabilities of old age are caused by chronic illnesses originating in early or middle age. Research into the causes of aging, particularly in regard to individual differences, is the greatest single need. Cardiovascular diseases, cancer, senile psychoses, arthritis, accidents, diabetes and tuberculosis are the more important of the afflictions, the prevention or amelioration of which will improve the health of the aged. Besides research into causes, the future must include devising better methods and setting up programs for the early detection of chronic diseases, rehabilitating sufferers from diseases such as arthritis and apoplexy, and providing for adequate institutional and home care of chronic disease patients.

THORACOPLASTY IN MIDDLE-AGED AND ELDERLY PATIENTS.

Källquist, I. *Acta tuberc. Scandinav.* **31:** 1, 1955 (Fasc. 1).

The response of 42 patients over 50 years of age to thoracoplasty is reported. All the patients were considered fit for major thoracic surgery. They had good respiratory function

and mainly unilateral disease. Thirty-nine patients had ipsilateral pulmonary cavitation on admission to the hospital, and in 20 cases contralateral infiltration was also present. Tubercle bacilli were found in the sputum of all but 1 patient on microscopy. Two patients died as a direct result of surgery. At the end of the observation period, which extended from January 1940 through June 1954, 29 of the 34 surviving patients showed negative bacillary findings. Five showed progression or residual cavity, but the roentgenograms had remained stable since operation in the other 29. Two deaths resulted from progressive tuberculosis, and 4 from nontuberculous causes. Preoperative therapy with antituberculosis drugs, given to 31 of the patients, was found effective, negative conversion of sputum occurring by the time of operation. Comparison of 18 patients who received premedication with 11 who did not clearly favored the treated group. Three years after thoracoplasty, 2 of the 16 survivors in the treated group had positive bacillary findings, compared with 3 of 8 survivors in the untreated group. The untreated group included the 2 fatal and 2 nonfatal cases of progression. Spirometric investigation of pulmonary function, carried out in 6 patients after operation, showed the diminution of function to be small in relation to the extent of the operation. In selected cases with good respiratory function, thoracoplasty is a safe and useful procedure in middle-aged and elderly persons.

"STROKES" VERSUS MASS LESIONS: DIFFERENTIAL DIAGNOSIS.

Lowrey, J. J. *Postgrad. Med.* **16:** 513 (Dec.) 1954.

Factors of importance in distinguishing cerebrovascular accidents, or "strokes," from mass lesions are discussed, and 2 case reports illustrating the diagnostic procedure are presented. A good history, including information on chronic disease, head trauma and onset and course of the illness, and an estimate of the speed of progression of the functional deficit by repeated neurologic examinations are the guides in the differential diagnosis. Age, arteriosclerosis, diabetes, hypertension, auricular fibrillation, coronary occlusion, kidney disease, and a tendency to bleed predispose toward cerebral thrombosis, hemorrhage and embolism. The physical examination should be complete. The neurologic examination can usually be performed by the average physician. The patient's state of consciousness, memory, orientation and ability to speak should be evaluated first. The head should be examined for signs of trauma. The examination should also include the cranial nerves in sequence, the eyes, and tests of muscle strength, sensation, coordination and propioception. Through careful and repeated examination of the reflexes, the speed of progression of lateralizing signs can be determined. Rapid progression of signs or symptoms unaccompanied by increased intracranial pressure is presumptive of a cerebrovascular accident. Tumors or chronic hematomas are likely to be characterized by a slow progression of signs until increased intracranial pressure occurs, after which the patient's condition deteriorates rapidly. When the diagnosis is obvious, appropriate treatment can be instituted. There is no justification for classifying questionable lesions as "strokes," when appropriate treatment might salvage certain patients. If a diagnosis cannot at first be made, signs of increased intracranial pressure are absent, and a stellate ganglion block is not indicated, the wisest course is to administer supportive treatment and vasodilator drugs and to observe the patient. The value of stellate ganglion blocks is questionable in the treatment of "strokes." Angiography has demonstrated that some patients with so-called cerebral thrombosis actually have a thrombosis of the internal carotid artery and in such cases there is more reason for the stellate ganglion block. If a progressive loss of function occurs in a patient under observation, or proper treatment demands an exact etiologic diagnosis, such procedures as roentgenograms of the chest and skull, lumbar puncture, angiograms, pneumoencephalograms or ventriculograms, or brain biopsy may be resorted to in order to establish the diagnosis. The choice among these will depend upon the suspected lesion and its location.

STUDY AND MANAGMENT OF UROLOGICAL PATIENTS WITH RENAL FAILURE.

Maluf, N. S. R. *J. Urol.* **72:** 1104 (Dec.) 1954.

In patients who have undergone prolonged obstruction and/or sustained infection in the urinary tract frequently irreversible chronic renal failure develops when these have been

removed. The patients may be kept comfortable for years and relatively free from acidosis by the oral intake of sodium acetate. The sodium ion acts as an available base for the urinary excretion of catabolic phosphate, sulfate and organic acids. Thus, extracellular fluid volume is maintained, diuresis promoted, and uremia diminished. If renal failure is not severe, potassium acetate may be added to combat the tendency for potassium loss from alkalosis and sodium intake. Calcium, as calcium lactate orally or calcium gluconate parenterally, must be given with the sodium acetate initially to prevent tetany from diminishing acidosis and low serum calcium concentration, but may not be necessary once the acidosis is overcome. The accumulation of phosphate can also be combatted by aluminum compounds orally. Uremia accompanied by nonobstructive staghorn renal calculi should be treated by the following *additional* measures: (a) a maintenance calcium diet (600 mg. daily), and (b) aluminum hydroxide or aluminum carbonate orally. The typical treatment of an acute exacerbation of uremia and acidosis in a patient with chronic renal failure aims to (a) correct the acidosis and raise the serum calcium level, (b) maintain normal serum sodium and chloride levels, (c) gradually overcome sodium depletion, and (d) replenish the potassium loss from prolonged acisosis. For parenteral replenishment of bicarbonate, the bicarbonate deficit should be calculated as though HCO_3 pervaded the entire body water and not the extracellular fluid alone. One gram of calcium gluconate should accompany every liter of M/6 sodium lactate. There is no advantage in correcting the anemia of uremia if the hemoglobin is 8 Gm. or more, unless major surgery is planned or hemorrhage is imminent. Case reports illustrate among other things that: 1) cation-exchange resins of the H^+-cycle orally or per rectum can lower the serum K^+ to normal prior to palliative surgery and may thus prevent disaster, 2) in advanced renal failure there may be a deficit in intracellular potassium but poor tolerance to potassium supplementation orally, 3) the serum creatinine and 24-hour creatinine clearance method is more efficacious than the blood urea nitrogen determination in measuring improvement in renal function, 4) with advanced renal damage due to prolonged obstruction by a hypertrophied prostate, the patient may become more uremic with preoperative catheter drainage but improve with suprapubic cystostomy, 5) in chronic uremia (a) there is either diminished erythropoiesis or no striking change in the cellular differential of bone marrow, and (b) the patient, when it is severe, is incapable of responding to allergins by an eosinophilic response of the bone marrow, 6) acidosis and an elevated serum potassium level may counterbalance the neuromuscular excitatory effect of hypocalcemia, 7) Gantrisin may induce anuria, apparently by nephrosis, 8) dehydration from lack of fluid intake can result in reversible severe oliguria or anuria in elderly persons, 9) persistent elevation of the blood urea nitrogen level, or hyperkaliemia in nontraumatic cases, in spite of a large urinary output, indicates advanced renal damage, and 10) fulminating pyelonephritis can still be fatal to elderly patients despite antibiotics. Factors that may cause negative balances of electrolyte and water in elderly individuals are, 1) renal tubular failure, 2) adrenocortical deficiency, 3) parenteral therapy with glucose and water, 4) sodium chloride restriction, 5) mercurial diuretics, and 6) failure of adequate tubular response to posterior pituitary antidiuretic hormone.

SOME IMPORTANT CLINICAL ASPECTS OF ESOPHAGEAL CARCINOMA: AN ANALYSIS OF 413 CASES.

Nightingale, E. J.; Svigals, C.; Mersheimer, W. L., and Boyd, L. J. *Am. J. Digest. Dis.* **21:** 341 (Dec.) 1954.

Esophageal carcinoma has a poor prognosis. The insidious onset and almost silent evolution explain the delayed recognition of this neoplasm. In order to stimulate interest in this disease, which is usually readily recognized by available and simple methods, an analysis, based on 413 cases is made with regard to: incidence, racial susceptibility, age and sex distribution, location, previous diagnoses, chief complaints, physical examination, delay in diagnosis, metastases, and causes of death. The chief complaints include dysphagia, vomiting, epigastric pain, chest pain, weight loss, lump in the neck, hemoptysis, cough,

hematemesis, stupor, enlarged abdomen, anorexia, changes in bowel habits, and hiccough. Stress is placed on their interpretation, in the hope that more early diagnoses will be made.

TWO CASES OF FULMINATING PNEUMONIA IN PATIENTS ON HORMONE THERAPY.
Page, J. A. *Brit. M. J.* **2:** 1334 (Dec. 4) 1954.

In 2 patients with rheumatoid arthritis, fulminating pneumonia caused death. One patient was being treated with cortisone and the other with ACTH for an acute exacerbation of arthritis. The hormone masked the symptoms of the severe infection. The second case was of particular interest because of the short duration of ACTH treatment and the low dosage—20 mg. of gel daily. At necropsy the adrenal and pituitary glands showed no gross histologic changes. The occurrence of infection during adrenocortical hormone administration can probably only be detected by constant clinical examination at short intervals. Antibiotic therapy is justifiable at the earliest signs or symptoms of infection.

THE EFFECT OF LIFE PROBLEMS AND CEREBRAL PATHOLOGY ON THE MENTAL HEALTH OF AGING PERSONS.
Potter, H. W., and Freiman, G. V. *New York State J. Med.* **54:** 2826 (Oct. 15) 1954.

A study of mental illnesses in 50 male patients between the ages of 60 and 87 years explored the impact of traumatic environmental experiences upon aged persons with some degree of cerebral infirmity. Particular attention was paid to the way in which external stresses operate to paralyze or distort established adaptive psychologic mechanisms and produce a psychotic state. The overt psychotic reactions of the patients studied were classified as acute or chronic in type. The neurologic examination showed no gross abnormalities but it was assumed that with senescence some organic brain changes had taken place. The study indicated that, in the elderly, cerebral frailty and inimical life situations act together to upset the psychologic homeostasis by setting up intolerable anxiety and by restricting the capacity to control anxiety within the framework of reality. Psychotic reactions in the aged cause the patient to deny reality in order to avoid the anxiety it produces and the patient's ties to reality are attenuated so that he is separated from the life in which he has invested all his mental energies. Psychotic reactions in an aged person should not be attributed solely to cerebral pathology. Comprehension of the emotional, physiologic and realistic life situations of aging people should afford new opportunities for prevention and treatment of mental invalidism in elderly people.

METASTASIS TO THE PENIS: REPORT OF FOUR CASES.
Poutasse, E. F. *J. Urol.* **72:** 1196 (Dec.) 1954.

Four cases of secondary involvement of the penis by metastasis from either carcinoma of the bladder or rectum are presented. All four patients died within a few months of the appearance of the penile metastasis. Secondary carcinoma of the penis is rare. The probable route of penile metastasis from the bladder, prostate or rectum is by retrograde flow of blood through the pudendal plexus to the deep dorsal vein of the penis. (Author's summary.)

TREATMENT OF ANGINA PECTORIS WITH CINCHONA ALKALOIDS.
Riseman, J. E. F.; Steinberg, L. A., and Altman, G. E. *Circulation* **10:** 809 (Dec.) 1954.

Studies demonstrating the value of quinidine sulfate in angina pectoris led to a search for related drugs that were equally effective but less toxic. The efficacy of 12 preparations in the treatment of angina pectoris was studied in 32 subjects. The methods of evaluation included the clinical response correlated with measurements of the exercise tolerance under standard conditions of cold, a study of electrocardiographic changes induced by exercise,

and a comparison with placebos, nitroglycerin and pentaerythritol tetranitrate. Results were analyzed in two groups of patients—those likely to respond to vasodilator therapy and those not likely to respond. Quinidine, quinine, cinchonidine and cinchamidine proved to be highly effective in some but not all patients with angina. The patients most likely to respond were those who responded well to nitroglycerin. Quinine sulfate, 0.3 to 0.4 Gm. every eight hours, appeared to be the drug of choice because of low toxicity, effectiveness, and low cost. It possesses less potential for cardiotoxic effects than quinidine. The effectiveness of the cinchona alkaloids in angina is due, at least in part, to vasodilation. The quinoline ring of the molecule probably primarily accounts for the therapeutic effect.

"ISOLATED" T-WAVE NEGATIVITY IN THE "ISCHEMIC PHASE" OF MYOCARDIAL INFARCTION IN MAN.

Schlant, R. C.; Levine, H. D., and Bailey, C. C. *Circulation* **10:** 829 (Dec.) 1954.

Inversion of the T waves, restricted to, or predominant in circumscribed areas of the precordium, may precede, herald or, at times, constitute an integral part of the electrocardiographic sequence of acute infarction of the anterior wall of the heart. These changes may remain fixed for long periods of time or show an instability toward or away from normality. In either case they may represent the clinical counterpart of an "ischemic" phase of myocardial infarction described in the experimental animal. The Q-T interval is generally normal when these changes are recorded but it may be shortened or lengthened. This experience emphasizes the need for protracted observation of patients showing these alterations and justifies scepticism toward regarding the changes, especially under clinically suspect circumstances, as normal variations. (From authors' conclusions.)

MYXOMETRA RESULTING FROM MUCOUS METAPLASIA OF THE ENDOMETRIUM.

Solomon, C., and Polishuk, W. *Am. J. Obst. & Gynec.* **68:** 1600 (Dec.) 1954.

A case of replacement of the endometrium by mucus-secreting glands is reported. This is apparently the only reported case of such glands occurring throughout the endometrium and invading the myometrium in the area of the fundus. The patient, a 64-year-old housewife, was admitted to the hospital because of a recent history of increasing ache in the lower abdomen and back, and of vaginal discharge of clear fluid occurring about once a month. The menopause had occurred uneventfully twenty-five years previously. The uterus was found to contain 300 cc. of clear albuminous fluid. After hysterectomy, microscopic examination of the endometrium revealed numerous mucus-secreting glands, some extending into the myometrium. No malignant cells or gross abnormalities were found. This case is apparently one of endometrial metaplasia due to postmenopausal changes in endocrine balance. The term myxometra is proposed by the authors to signify the accumulation of mucoid material in the uterine cavity.